

Desai, A.  
10/817312

10/817312

FILE 'REGISTRY' ENTERED AT 12:22:27 ON 07 APR 2005  
ACT DESAIA817REG/A

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L1 (      8)SEA FILE=REGISTRY ABB=ON PLU=ON (SILDENFIL OR ZAPRINAST O
L2 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "GF 196960"/CN
L3 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON ("E 8010"/CN OR "E 8010 (
L4 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "E 4010"/CN
L5 (      2)SEA FILE=REGISTRY ABB=ON PLU=ON "BAY 38-3045"/CN OR "BAY
L6 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 51866"/CN
L7 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 59498"/CN
L8 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "UK 343664"/CN
L9 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON 5E3623/CN
L10 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON 5E3569/CN
L11 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON 5E3657/CN
L12 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON "KS 505A"/CN
L13 (     2)SEA FILE=REGISTRY ABB=ON PLU=ON ("YC 1"/CN OR "YC 1 (ELEC
L14 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON "BMS 341400"/CN
L15 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON "WIN 61691"/CN
L16 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON "FR 226807"/CN
L17 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON SILDENAFIL/CN
L18 (    72)SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE/CN OR
L19 (     2)SEA FILE=REGISTRY ABB=ON PLU=ON ("PHOSPHODIESTERASE 5"/CN
L20 (    71)SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE/CN OR
L21 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON "IC 351"/CN
L22 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON TADALAFIL/CN
L23 (     2)SEA FILE=REGISTRY ABB=ON PLU=ON ("AWD 12-171"/CN OR "AWD
L24 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON "E 4021"/CN
L25 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON FURAZLOCILLIN/CN
L26 (    104)SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2 OR L3 OR L4 OR L
L27 (     11)SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE 1 OR P
L28 (    148)SEA FILE=REGISTRY ABB=ON PLU=ON ?"ETHOXY-5-(4-METHYL-1-PI
L29 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON ?"ETHOXY-5-MORPHOLINOACET
L30 (    107)SEA FILE=REGISTRY ABB=ON PLU=ON ?"DIHYDRO-7H-PYRAZOLO"?/C
L31 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON ?"METHYL-7-PROPYL-3H-IMID
L32 (     26)SEA FILE=REGISTRY ABB=ON PLU=ON ?"HEXAHYDRO-2-(4-(TRIFLUO
L33 (     1)SEA FILE=REGISTRY ABB=ON PLU=ON ?"CHLOROBENZYL-2-PROPYLIN
L34 (    2944)SEA FILE=REGISTRY ABB=ON PLU=ON ?"CHLORO-2-QUINOLIN"?/CNS
L35 (    5216)SEA FILE=REGISTRY ABB=ON PLU=ON ?"HEXAHYDRO-5-METHYL"?/CN
L36 (     8)SEA FILE=REGISTRY ABB=ON PLU=ON ?"PHENYLMETHYL) SPIRO (CYCL
L37 (     4)SEA FILE=REGISTRY ABB=ON PLU=ON ?"TETRAHYDRO-2H-PYRROLO"?
L38 (    8563)SEA FILE=REGISTRY ABB=ON PLU=ON L26 OR L27 OR L28 OR L29
-----
L39      93 S (LETROZOLE OR ANASTROZOLE OR VOROZOLE OR FOLLICLE STIMULA
L40     112 S CHORIONIC GONADOTROPIN?/CN
L41     2980 S LUTEINIZING HORMONE?/CN
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FILE 'HCAPLUS' ENTERED AT 12:24:09 ON 07 APR 2005

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L1 (      8)SEA FILE=REGISTRY ABB=ON PLU=ON (SILDENFIL OR ZAPRINAST
      OR DIPYRIDAMOLE OR VARDENAFIL OR PHARMAPROJECTS 4516 OR
      PHARMAPROJECTS 5051 OR PHARMAPROJECTS 5064 OR PHARMAPROJECT
      S 5069 OR "GF-196960" OR "E-8010" OR "E-4010" OR "BAY-38-30
      45" OR "BAY-38-9456" OR VINPOCETINE OR "SCH-51866" OR
      "SCH-59498" OR "AWD-12-217")/CN
L2 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "GF 196960"/CN
L3 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON ("E 8010"/CN OR "E 8010
      (ENZYME INHIBITOR)"/CN)
L4 (      1)SEA FILE=REGISTRY ABB=ON PLU=ON "E 4010"/CN
L5 (      2)SEA FILE=REGISTRY ABB=ON PLU=ON "BAY 38-3045"/CN OR "BAY
      38-9456"/CN
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Searcher : Shears 571-272-2528

L6 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 51866"/CN  
 L7 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 59498"/CN  
 L8 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "UK 343664"/CN  
 L9 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON 5E3623/CN  
 L10 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON 5E3569/CN  
 L11 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON 5E3657/CN  
 L12 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "KS 505A"/CN  
 L13 ( 2)SEA FILE=REGISTRY ABB=ON PLU=ON ("YC 1"/CN OR "YC 1  
 (ELECTROPLATING ADDITIVE)"/CN OR "YC 1 (PHARMACEUTICAL)"/CN  
 )  
 L14 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "BMS 341400"/CN  
 L15 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "WIN 61691"/CN  
 L16 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON "FR 226807"/CN  
 L17 ( 1)SEA FILE=REGISTRY ABB=ON PLU=ON SILDENAFIL/CN  
 L18 ( 72)SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE/CN OR  
 "PHOSPHODIESTERASE (BDELLOVIBRIO BACTERIOVORUS STRAIN  
 HD100 GENE GLPQ)"/CN OR "PHOSPHODIESTERASE (BIFIDOBACTERIUM  
 LONGUM STRAIN NCC2705 GENE BL1252)"/CN OR "PHOSPHODIESTERA  
 SE (BURKHOLDERIA PSEUDOMALLEI STRAIN K96243)"/CN OR  
 "PHOSPHODIESTERASE (CANARYPOX VIRUS STRAIN ATCC-VR-111  
 STRAIN WHEATLEY\_C93 GENE CNPV048 SEQUENCE HOMOLOG)"/CN OR  
 "PHOSPHODIESTERASE (CYANOPHAGE S-2L 58-AMINO ACID)"/CN OR  
 "PHOSPHODIESTERASE (EQUUS CABALLUS GENE PDE6G GAMMA  
 SUBUNIT)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS GENE  
 FPV030)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS ISOLATE  
 HP1-438 MUNICH CLONE FP9 GENE FP9.030)"/CN OR "PHOSPHODIEST  
 ERASE (HUMAN BRAIN)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE  
 H6.1 ISOENZYME IV)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE  
 PDEU7 ISOENZYME IVC)"/CN OR "PHOSPHODIESTERASE (HUMAN  
 CLONE PPDE32 TYPE IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIE  
 STERASE (HUMAN CLONE PPDE43 TYPE IV GENE DPDE3 ISOFORM)"/CN  
 OR "PHOSPHODIESTERASE (HUMAN CLONE PPDE46 TYPE IV GENE  
 DPDE2)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PTM72 TYPE  
 IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIESTERASE (HUMAN  
 FETAL BRAIN (18 WEEKS) GENE PDE7B ISOENZYME 7B)"/CN OR  
 "PHOSPHODIESTERASE (HUMAN GENE A ISOENZYME IUA)"/CN OR  
 "PHOSPHODIESTERASE (HUMAN GENE ASM3A ISOENZYME 3A)"/CN OR  
 "PHOSPHODIESTERASE (HUMAN GENE ASML3B ACID SPHINGOMYELINASE  
 -LIKE)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE ASML3B  
 ISOENZYME 3B)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE B  
 ISOENZYME IUB)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE D  
 TYPE ISOENZYME IUD)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE  
 PDE4B ISOENZYME PDE4B1)"/CN OR "PHOSPHODIESTERASE (HUMAN  
 GENE PDE4B ISOENZYME PDE4B2)"/CN OR "PHOSPHODIESTERASE  
 (HUMAN GENE PDE4B ISOENZYME PDE4B3)"/CN OR "PHOSPHODIESTERA  
 SE (HUMAN GENE PDNP2 REDUCED)"/CN OR "PHOSPHODIESTERASE  
 (HUMAN HERPESVIRUS 6 VARIANT A STRAIN U1102 GENE U70)"/CN  
 OR "PHOSPHODIESTERASE (HUMAN ISOENZYME IVC FRAGMENT)"/CN  
 OR "PHOSPHODIESTERASE (HUMAN PLACENTA BRAIN ISOENZYME  
 21)"/CN OR "PHOSPHODIESTERASE (HUMAN)"/CN OR "  
 L19 ( 2)SEA FILE=REGISTRY ABB=ON PLU=ON ("PHOSPHODIESTERASE  
 5"/CN OR "PHOSPHODIESTERASE 6"/CN OR "PHOSPHODIESTERASE 6  
 (RATTUS NORVEGICUS STRAIN WISTAR F-SUBUNIT)"/CN)  
 L20 ( 71)SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE/CN OR  
 "PHOSPHODIESTERASE (BDELLOVIBRIO BACTERIOVORUS STRAIN  
 HD100 GENE GLPQ)"/CN OR "PHOSPHODIESTERASE (BIFIDOBACTERIUM  
 LONGUM STRAIN NCC2705 GENE BL1252)"/CN OR "PHOSPHODIESTERA  
 SE (BURKHOLDERIA PSEUDOMALLEI STRAIN K96243)"/CN OR  
 "PHOSPHODIESTERASE (CANARYPOX VIRUS STRAIN ATCC-VR-111

STRAIN WHEATLEY\_C93 GENE CNPV048 SEQUENCE HOMOLOG)"/CN OR  
 "PHOSPHODIESTERASE (CYANOPHAGE S-2L 58-AMINO ACID)"/CN OR  
 "PHOSPHODIESTERASE (EQUUS CABALLUS GENE PDE6G GAMMA  
 SUBUNIT)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS GENE  
 FPV030)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS ISOLATE  
 HP1-438 MUNICH CLONE FP9 GENE FP9.030)"/CN OR "PHOSPHODIEST  
 ERASE (HUMAN BRAIN)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE  
 H6.1 ISOENZYME IV)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE  
 PDEU7 ISOENZYME IVC)"/CN OR "PHOSPHODIESTERASE (HUMAN  
 CLONE PPDE32 TYPE IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIE  
 STERASE (HUMAN CLONE PPDE43 TYPE IV GENE DPDE3 ISOFORM)"/CN  
 OR "PHOSPHODIESTERASE (HUMAN CLONE PPDE46 TYPE IV GENE  
 DPDE2)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PTM72 TYPE  
 IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIESTERASE (HUMAN  
 FETAL BRAIN (18 WEEKS) GENE PDE7B ISOENZYME 7B)"/CN OR  
 "PHOSPHODIESTERASE (HUMAN GENE A ISOENZYME IUA)"/CN OR  
 "PHOSPHODIESTERASE (HUMAN GENE ASM3A ISOENZYME 3A)"/CN OR  
 "PHOSPHODIESTERASE (HUMAN GENE ASML3B ACID SPHINGOMYELINASE  
 -LIKE)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE ASML3B  
 ISOENZYME 3B)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE B  
 ISOENZYME IUB)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE D  
 TYPE ISOENZYME IUD)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE  
 PDE4B ISOENZYME PDE4B1)"/CN OR "PHOSPHODIESTERASE (HUMAN  
 GENE PDE4B ISOENZYME PDE4B2)"/CN OR "PHOSPHODIESTERASE  
 (HUMAN GENE PDE4B ISOENZYME PDE4B3)"/CN OR "PHOSPHODIESTERA  
 SE (HUMAN GENE PDNP2 REDUCED)"/CN OR "PHOSPHODIESTERASE  
 (HUMAN HERPESVIRUS 6 VARIANT A STRAIN U1102 GENE U70)"/CN  
 OR "PHOSPHODIESTERASE (HUMAN ISOENZYME IVC FRAGMENT)"/CN  
 OR "PHOSPHODIESTERASE (HUMAN PLACENTA BRAIN ISOENZYME  
 21)"/CN OR "PHOSPHODIESTERASE (HUMAN)"/CN OR "

L21 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "IC 351"/CN  
 L22 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON TADALAFIL/CN  
 L23 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON ("AWD 12-171"/CN OR "AWD  
 12-217"/CN)  
 L24 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "E 4021"/CN  
 L25 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON FURAZLOCILLIN/CN  
 L26 ( 104) SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2 OR L3 OR L4 OR  
 L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR  
 L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR  
 L22 OR L23 OR L24 OR L25  
 L27 ( 11) SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE 1 OR  
 PHOSPHODIESTERASE 5 OR PHOSPHODIESTERASE 6 OR PHOSPHODIESTE  
 RASE 7 OR PHOSPHODIESTERASE 9 OR PHOSPHODIESTERASE 10 OR  
 PHOSPHODIESTERASE 4 OR PICLAMILAST OR ROFLUMILAST OR  
 ARIFLO OR FILAMINAST OR MESOPRAM OR D4418 OR D 4418 OR  
 AROFYLLINE OR CL 1044)/CN  
 L28 ( 148) SEA FILE=REGISTRY ABB=ON PLU=ON ?"ETHOXY-5-(4-METHYL-1-PI  
 PERAZINYL"?/CNS  
 L29 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ?"ETHOXY-5-MORPHOLINOACET  
 YL"?/CNS  
 L30 ( 107) SEA FILE=REGISTRY ABB=ON PLU=ON ?"DIHYDRO-7H-PYRAZOLO"?/C  
 NS  
 L31 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ?"METHYL-7-PROPYL-3H-IMID  
 AZO"?/CNS  
 L32 ( 26) SEA FILE=REGISTRY ABB=ON PLU=ON ?"HEXAHYDRO-2-(4-(TRIFLUO  
 ROMETHYL"?/CNS  
 L33 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ?"CHLOROBENZYL-2-PROPYLIN  
 DOLE"?/CNS  
 L34 ( 2944) SEA FILE=REGISTRY ABB=ON PLU=ON ?"CHLORO-2-QUINOLIN"?/CNS

L35 ( 5216) SEA FILE=REGISTRY ABB=ON PLU=ON ?"HEXAHYDRO-5-METHYL"?/CN  
 S  
 L36 ( 8) SEA FILE=REGISTRY ABB=ON PLU=ON ?"PHENYLMETHYL" SPIRO (CYCL  
 OPENTANE"?/CNS  
 L37 ( 4) SEA FILE=REGISTRY ABB=ON PLU=ON ?"TETRAHYDRO-2H-PYRROLO"?  
 /CNS  
 L38 8563 SEA FILE=REGISTRY ABB=ON PLU=ON L26 OR L27 OR L28 OR L29  
 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37  
 L39 93 SEA FILE=REGISTRY ABB=ON PLU=ON (LETROZOLE OR ANASTROZOLE  
 OR VOROZOLE OR FOLLICLE STIMULATING HORMONE? OR FSH?)/CN  
 L40 112 SEA FILE=REGISTRY ABB=ON PLU=ON CHORIONIC GONADOTROPIN?/C  
 N  
 L41 2980 SEA FILE=REGISTRY ABB=ON PLU=ON LUTEINIZING HORMONE?/CN  
 L42 5615 SEA FILE=HCAPLUS ABB=ON PLU=ON SILDENAFIL OR ZAPRINAST  
 OR DIPYRIDAMOLE OR DI PYRIDAMOLE OR TADALAFIL OR IC351 OR  
 IC 351 OR VARDENAFIL OR FURAZ!OCILLIN OR (PHARMAPROJECT OR  
 PHARMA PROJECT) (1W) (4516 OR 5051 OR 5064 OR 5069) OR  
 GF196960 OR GF 196960 OR "E" (W) (8010 OR 4010) OR "E8010"  
 OR "E4010"  
 L43 325 SEA FILE=HCAPLUS ABB=ON PLU=ON BAY(W) 38(W) (3045 OR 9456)  
 OR VINPOCETIN OR SCH51866 OR SCH59498 OR SCH(W) (51866 OR  
 59498) OR AWD(W) 12(W) (171 OR 217) OR BMS 341400 OR  
 UK(W) (343664 OR 343 664) OR "5E" (W) (3623 OR 3569 OR 3657)  
 OR "E4012" OR KS505A OR KS 505A OR YC(W) (1 OR I) OR YCI OR  
 YC1 OR 323951  
 L44 2300 SEA FILE=HCAPLUS ABB=ON PLU=ON WIN 61691 OR WIN61691 OR  
 FR226807 OR FR 226807 OR 461317 OR 462503 OR 461321 OR  
 461324 OR 466146 OR (PDE OR PHOSPHODIESTERASE OR PHOSPHO(W)  
 (DIESTERASE OR DI ESTERASE) OR PHOSPHODI ESTERASE) (W) (1 OR  
 5 OR 6 OR 7 OR 9 OR 10 OR 4) OR PDE1 OR PDE5 OR PDE6 OR  
 PDE7 OR PDE9 OR PDE10 OR PDE4  
 L45 178 SEA FILE=HCAPLUS ABB=ON PLU=ON PICLAMILAST OR ROFLUMILAST  
 OR ARIFLO OR FILAMINAST OR MESOPRAM OR D4418 OR D 4418 OR  
 AROFYLLINE OR CL1044 OR CL 1044  
 L46 103 SEA FILE=HCAPLUS ABB=ON PLU=ON (7H(1W) PYRAZOLO) (S) (4(2W) (  
 PYRIMIDIN?)) OR INDOLE(W) 1(W) 4(W) DIONE OR (METHYL OR  
 ME) (W) 7(W) (PROPYL OR PR) (2W) IMIDAZO? OR (4(W) BROMO) (S) PYRID  
 AZIONE OR (3(W) (BENZODIOXOL OR BENZO DIOXOL)) (S) QUINOZOLIN?  
 OR (9(W) 9(1W) (HEXAHYDRO OR HEXA HYDRO)) (S) PURIN?  
 L47 131 SEA FILE=HCAPLUS ABB=ON PLU=ON (PROPYLINDOLE OR (PR OR  
 PROPYL) (W) INDOLE) (S) (6(W) CARBOXYLATE) OR (4(W) BROMO) (S) PYRI  
 DAZINONE OR (5(W) (MORPHOLINOACETYL? OR MORPHOLINO(W) (ACETYL  
 OR AC)) (S) PYRAZOL? OR (3(W) (BENZODIOXOL OR BENZO  
 DIOXOL)) (S) PIPERIDIN? OR ((HEXAHYDRO OR HEXA HYDRO) (W) 5(W) (  
 METHYL OR ME)) (S) IMIDAZO?  
 L48 433 SEA FILE=HCAPLUS ABB=ON PLU=ON ((5(W) (METHYL OR ME)) (S) SP  
 IRO?) (S) IMIDAZO? OR (3(W) (BENZODIOXOL? OR BENZO DIOXOL?)) (S)  
 ) PYRROLO? OR VINPOCETINE OR 5E3623 OR 5E3569 OR 5E3657  
 L49 8251 SEA FILE=HCAPLUS ABB=ON PLU=ON L42 OR L43 OR L44 OR L45  
 OR L46 OR L47 OR L48 OR (PDE OR PHOSPHODIESTERASE OR  
 PHOSPHO DIESTERASE) (W) (1 OR 5 OR 6 OR 7 OR 9 OR 10 OR 4)  
 L50 129 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L49) AND (L39 OR  
 FSH OR FOLLICLE STIMULAT? HORMONE OR FOLLITROPIN OR  
 LETROZOLE OR ANASTROZOLE OR VOROZOLE)  
 L51 60 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L49) AND (L40 OR  
 HCG OR CHORIONIC GONADOTROPIN)  
 L52 141 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L49) AND (L41 OR  
 LH OR LUTEINIZING HORMONE)



L53 26 SEA FILE=HCAPLUS ABB=ON PLU=ON (L50 OR L51 OR L52) AND  
((OOCYTE OR OVOCYT?) (S) PRODUC? OR (OVARI## OR ATRETIC OR  
GRAAFIAN OR FOLLICUL?) (S) (HYPERSTIMULAT? OR STIMULAT?) OR  
OVULAT?)

L1 ( 8) SEA FILE=REGISTRY ABB=ON PLU=ON (SILDENFIL OR ZAPRINAST  
OR DIPYRIDAMOLE OR VARDENAFIL OR PHARMAPROJECTS 4516 OR  
PHARMAPROJECTS 5051 OR PHARMAPROJECTS 5064 OR PHARMAPROJECT  
S 5069 OR "GF-196960" OR "E-8010" OR "E-4010" OR "BAY-38-30  
45" OR "BAY-38-9456" OR VINPOCETINE OR "SCH-51866" OR  
"SCH-59498" OR "AWD-12-217")/CN

L2 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "GF 196960"/CN

L3 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ("E 8010"/CN OR "E 8010  
(ENZYME INHIBITOR)"/CN)

L4 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "E 4010"/CN

L5 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON "BAY 38-3045"/CN OR "BAY  
38-9456"/CN

L6 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 51866"/CN

L7 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 59498"/CN

L8 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "UK 343664"/CN

L9 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON 5E3623/CN

L10 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON 5E3569/CN

L11 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON 5E3657/CN

L12 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "KS 505A"/CN

L13 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON ("YC 1"/CN OR "YC 1  
(ELECTROPLATING ADDITIVE)"/CN OR "YC 1 (PHARMACEUTICAL)"/CN  
)

L14 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "BMS 341400"/CN

L15 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "WIN 61691"/CN

L16 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "FR 226807"/CN

L17 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON SILDENAFIL/CN

L18 ( 72) SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE/CN OR  
"PHOSPHODIESTERASE (BDELLOVIBRIO BACTERIOVORUS STRAIN  
HD100 GENE GLPQ)"/CN OR "PHOSPHODIESTERASE (BIFIDOBACTERIUM  
LONGUM STRAIN NCC2705 GENE BL1252)"/CN OR "PHOSPHODIESTERA  
SE (BURKHOLDERIA PSEUDOMALLEI STRAIN K96243)"/CN OR  
"PHOSPHODIESTERASE (CANARYPOX VIRUS STRAIN ATCC-VR-111  
STRAIN WHEATLEY\_C93 GENE CNPV048 SEQUENCE HOMOLOG)"/CN OR  
"PHOSPHODIESTERASE (CYANOPHAGE S-2L 58-AMINO ACID)"/CN OR  
"PHOSPHODIESTERASE (EQUUS CABALLUS GENE PDE6G GAMMA  
SUBUNIT)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS GENE  
FPV030)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS ISOLATE  
HP1-438 MUNICH CLONE FP9 GENE FP9.030)"/CN OR "PHOSPHODIEST  
ERASE (HUMAN BRAIN)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE  
H6.1 ISOENZYME IV)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE  
PDEU7 ISOENZYME IVC)"/CN OR "PHOSPHODIESTERASE (HUMAN  
CLONE PPDE32 TYPE IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIE  
STERASE (HUMAN CLONE PPDE43 TYPE IV GENE DPDE3 ISOFORM)"/CN  
OR "PHOSPHODIESTERASE (HUMAN CLONE PPDE46 TYPE IV GENE  
DPDE2)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PTM72 TYPE  
IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIESTERASE (HUMAN  
FETAL BRAIN (18 WEEKS) GENE PDE7B ISOENZYME 7B)"/CN OR  
"PHOSPHODIESTERASE (HUMAN GENE A ISOENZYME IUA)"/CN OR  
"PHOSPHODIESTERASE (HUMAN GENE ASM3A ISOENZYME 3A)"/CN OR  
"PHOSPHODIESTERASE (HUMAN GENE ASML3B ACID SPHINGOMYELINASE  
-LIKE)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE ASML3B  
ISOENZYME 3B)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE B

- ISOENZYME IUB)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE D TYPE ISOENZYME IUD)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDE4B ISOENZYME PDE4B1)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDE4B ISOENZYME PDE4B2)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDE4B ISOENZYME PDE4B3)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDNP2 REDUCED)"/CN OR "PHOSPHODIESTERASE (HUMAN HERPESVIRUS 6 VARIANT A STRAIN U1102 GENE U70)"/CN OR "PHOSPHODIESTERASE (HUMAN ISOENZYME IVC FRAGMENT)"/CN OR "PHOSPHODIESTERASE (HUMAN PLACENTA BRAIN ISOENZYME 21)"/CN OR "PHOSPHODIESTERASE (HUMAN)"/CN OR "
- L19 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON ("PHOSPHODIESTERASE 5"/CN OR "PHOSPHODIESTERASE 6"/CN OR "PHOSPHODIESTERASE 6 (RATTUS NORVEGICUS STRAIN WISTAR Γ-SUBUNIT)"/CN)
- L20 ( 71) SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE/CN OR "PHOSPHODIESTERASE (BDELLOVIBRIO BACTERIOVORUS STRAIN HD100 GENE GLPQ)"/CN OR "PHOSPHODIESTERASE (BIFIDOBACTERIUM LONGUM STRAIN NCC2705 GENE BL1252)"/CN OR "PHOSPHODIESTERASE (BURKHOLDERIA PSEUDOMALLEI STRAIN K96243)"/CN OR "PHOSPHODIESTERASE (CANARYPOX VIRUS STRAIN ATCC-VR-111 STRAIN WHEATLEY\_C93 GENE CNPV048 SEQUENCE HOMOLOG)"/CN OR "PHOSPHODIESTERASE (CYANOPHAGE S-2L 58-AMINO ACID)"/CN OR "PHOSPHODIESTERASE (EQUUS CABALLUS GENE PDE6G GAMMA SUBUNIT)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS GENE FPV030)"/CN OR "PHOSPHODIESTERASE (FOWLPOX VIRUS ISOLATE HP1-438 MUNICH CLONE FP9 GENE FP9.030)"/CN OR "PHOSPHODIESTERASE (HUMAN BRAIN)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE H6.1 ISOENZYME IV)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PDEU7 ISOENZYME IVC)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PPDE32 TYPE IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PPDE43 TYPE IV GENE DPDE3 ISOFORM)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PPDE46 TYPE IV GENE DPDE2)"/CN OR "PHOSPHODIESTERASE (HUMAN CLONE PTM72 TYPE IV GENE DPDE4 ISOFORM)"/CN OR "PHOSPHODIESTERASE (HUMAN FETAL BRAIN (18 WEEKS) GENE PDE7B ISOENZYME 7B)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE A ISOENZYME IUA)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE ASM3A ISOENZYME 3A)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE ASML3B ACID SPHINGOMYELINASE-LIKE)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE ASML3B ISOENZYME 3B)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE B ISOENZYME IUB)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE D TYPE ISOENZYME IUD)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDE4B ISOENZYME PDE4B1)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDE4B ISOENZYME PDE4B2)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDE4B ISOENZYME PDE4B3)"/CN OR "PHOSPHODIESTERASE (HUMAN GENE PDNP2 REDUCED)"/CN OR "PHOSPHODIESTERASE (HUMAN HERPESVIRUS 6 VARIANT A STRAIN U1102 GENE U70)"/CN OR "PHOSPHODIESTERASE (HUMAN ISOENZYME IVC FRAGMENT)"/CN OR "PHOSPHODIESTERASE (HUMAN PLACENTA BRAIN ISOENZYME 21)"/CN OR "PHOSPHODIESTERASE (HUMAN)"/CN OR "
- L21 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "IC 351"/CN
- L22 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON TADALAFIL/CN
- L23 ( 2) SEA FILE=REGISTRY ABB=ON PLU=ON ("AWD 12-171"/CN OR "AWD 12-217"/CN)
- L24 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON "E 4021"/CN
- L25 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON FURAZLOCILLIN/CN
- L26 ( 104) SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25

L27 ( 11) SEA FILE=REGISTRY ABB=ON PLU=ON (PHOSPHODIESTERASE 1 OR  
 PHOSPHODIESTERASE 5 OR PHOSPHODIESTERASE 6 OR PHOSPHODIESTE  
 RASE 7 OR PHOSPHODIESTERASE 9 OR PHOSPHODIESTERASE 10 OR  
 PHOSPHODIESTERASE 4 OR PICLAMILAST OR ROFLUMILAST OR  
 ARIFLO OR FILAMINAST OR MESOPRAM OR D4418 OR D 4418 OR  
 AROFYLLINE OR CL 1044)/CN  
 L28 ( 148) SEA FILE=REGISTRY ABB=ON PLU=ON ?"ETHOXY-5-(4-METHYL-1-PI  
 PERAZINYL"?/CNS  
 L29 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ?"ETHOXY-5-MORPHOLINOACET  
 YL"?/CNS  
 L30 ( 107) SEA FILE=REGISTRY ABB=ON PLU=ON ?"DIHYDRO-7H-PYRAZOLO"?/C  
 NS  
 L31 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ?"METHYL-7-PROPYL-3H-IMID  
 AZO"?/CNS  
 L32 ( 26) SEA FILE=REGISTRY ABB=ON PLU=ON ?"HEXAHYDRO-2-(4-(TRIFLUO  
 ROMETHYL"?/CNS  
 L33 ( 1) SEA FILE=REGISTRY ABB=ON PLU=ON ?"CHLOROBENZYL-2-PROPYLIN  
 DOLE"?/CNS  
 L34 ( 2944) SEA FILE=REGISTRY ABB=ON PLU=ON ?"CHLORO-2-QUINOLIN"?/CNS  
 L35 ( 5216) SEA FILE=REGISTRY ABB=ON PLU=ON ?"HEXAHYDRO-5-METHYL"?/CN  
 S  
 L36 ( 8) SEA FILE=REGISTRY ABB=ON PLU=ON ?"PHENYLMETHYL) SPIRO (CYCL  
 OPENTANE"?/CNS  
 L37 ( 4) SEA FILE=REGISTRY ABB=ON PLU=ON ?"TETRAHYDRO-2H-PYRROLO"?  
 /CNS  
 L38 8563 SEA FILE=REGISTRY ABB=ON PLU=ON L26 OR L27 OR L28 OR L29  
 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37  
 L39 93 SEA FILE=REGISTRY ABB=ON PLU=ON (LETROZOLE OR ANASTROZOLE  
 OR VOROZOLE OR FOLLICLE STIMULATING HORMONE? OR FSH?)/CN  
 L40 112 SEA FILE=REGISTRY ABB=ON PLU=ON CHORIONIC GONADOTROPIN?/C  
 N  
 L41 2980 SEA FILE=REGISTRY ABB=ON PLU=ON LUTEINIZING HORMONE?/CN  
 L42 5615 SEA FILE=HCAPLUS ABB=ON PLU=ON SILDENAFIL OR ZAPRINAST  
 OR DIPYRIDAMOLE OR DI PYRIDAMOLE OR TADALAFIL OR IC351 OR  
 IC 351 OR VARDENAFIL OR FURAZ!OCILLIN OR (PHARMAPROJECT OR  
 PHARMA PROJECT) (1W) (4516 OR 5051 OR 5064 OR 5069) OR  
 GF196960 OR GF 196960 OR "E" (W) (8010 OR 4010) OR "E8010"  
 OR "E4010"  
 L43 325 SEA FILE=HCAPLUS ABB=ON PLU=ON BAY(W) 38(W) (3045 OR 9456)  
 OR VINPOCETIN OR SCH51866 OR SCH59498 OR SCH(W) (51866 OR  
 59498) OR AWD(W) 12(W) (171 OR 217) OR BMS 341400 OR  
 UK(W) (343664 OR 343 664) OR "5E" (W) (3623 OR 3569 OR 3657)  
 OR "E4012" OR KS505A OR KS 505A OR YC(W) (1 OR I) OR YCI OR  
 YC1 OR 323951  
 L44 2300 SEA FILE=HCAPLUS ABB=ON PLU=ON WIN 61691 OR WIN61691 OR  
 FR226807 OR FR 226807 OR 461317 OR 462503 OR 461321 OR  
 461324 OR 466146 OR (PDE OR PHOSPHODIESTERASE OR PHOSPHO(W)  
 (DIESTERASE OR DI ESTERASE) OR PHOSPHODI ESTERASE) (W) (1 OR  
 5 OR 6 OR 7 OR 9 OR 10 OR 4) OR PDE1 OR PDE5 OR PDE6 OR  
 PDE7 OR PDE9 OR PDE10 OR PDE4  
 L45 178 SEA FILE=HCAPLUS ABB=ON PLU=ON PICLAMILAST OR ROFLUMILAST  
 OR ARIFLO OR FILAMINAST OR MESOPRAM OR D4418 OR D 4418 OR  
 AROFYLLINE OR CL1044 OR CL 1044  
 L46 103 SEA FILE=HCAPLUS ABB=ON PLU=ON (7H(1W) PYRAZOLO) (S) (4(2W) (P  
 YRIMIDIN?)) OR INDOLE(W) 1(W) 4(W) DIONE OR (METHYL OR  
 ME) (W) 7(W) (PROPYL OR PR) (2W) IMIDAZO? OR (4(W) BROMO) (S) PYRID  
 AZIONE OR (3(W) (BENZODIOXOL OR BENZO DIOXOL)) (S) QUINOZOLIN?  
 OR (9(W) 9(1W) (HEXAHYDRO OR HEXA HYDRO)) (S) PURIN?

L47 131 SEA FILE=HCAPLUS ABB=ON PLU=ON (PROPYLINDOLE OR (PR OR  
 PROPYL) (W) INDOLE) (S) (6 (W) CARBOXYLATE) OR (4 (W) BROMO) (S) PYRI  
 DAZINONE OR (5 (W) (MORPHOLINOACETYL? OR MORPHOLINO (W) (ACETYL  
 OR AC)) (S) PYRAZOL? OR (3 (W) (BENZODIOXOL OR BENZO  
 DIOXOL)) (S) PIPERIDIN? OR ((HEXAHYDRO OR HEXA HYDRO) (W) 5 (W) (METHYL OR ME)) (S) IMIDAZO?

L48 433 SEA FILE=HCAPLUS ABB=ON PLU=ON ((5 (W) (METHYL OR ME)) (S) SP  
 IRO?) (S) IMIDAZO? OR (3 (W) (BENZODIOXOL? OR BENZO DIOXOL?)) (S  
 ) PYRROLO? OR VINPOCETINE OR 5E3623 OR 5E3569 OR 5E3657

L49 8251 SEA FILE=HCAPLUS ABB=ON PLU=ON L42 OR L43 OR L44 OR L45  
 OR L46 OR L47 OR L48 OR (PDE OR PHOSPHODIESTERASE OR  
 PHOSPHO DIESTERASE) (W) (1 OR 5 OR 6 OR 7 OR 9 OR 10 OR 4)

L50 129 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L49) AND (L39 OR  
 FSH OR FOLLICLE STIMULAT? HORMONE OR FOLLITROPIN OR  
 LETROZOLE OR ANASTROZOLE OR VOROZOLE)

L51 60 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L49) AND (L40 OR  
 HCG OR CHORIONIC GONADOTROPIN)

L52 141 SEA FILE=HCAPLUS ABB=ON PLU=ON (L38 OR L49) AND (L41 OR  
 LH OR LUTEINIZING HORMONE)

L54 19 SEA FILE=HCAPLUS ABB=ON PLU=ON (L50 OR L51 OR L52) AND  
 FEMALE

L55 11 SEA FILE=HCAPLUS ABB=ON PLU=ON L54 AND (STERIL? OR  
 INFERTIL? OR FERTIL?)

L56 29 L53 OR L55

L56 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 05 Jan 2005

ACCESSION NUMBER: 2005:7984 HCAPLUS

DOCUMENT NUMBER: 142:274219

TITLE: The phosphodiesterase 3 inhibitor ORG 9935  
 inhibits oocyte maturation during gonadotropin-  
**stimulated ovarian** cycles in  
 rhesus macaques

AUTHOR(S): Jensen, Jeffrey T.; Zelinski-Wooten, Mary B.;  
 Schwinof, Kristine M.; Vance, Jessica E.;  
 Stouffer, Richard L.

CORPORATE SOURCE: Department of Obstetrics and Gynecology and  
 Division of Reproductive Sciences, Oregon National  
 Primate Research Center, Oregon Health and Science  
 University, Portland, OR, 97239, USA

SOURCE: Contraception (2005), 71(1), 68-73

CODEN: CCPTAY; ISSN: 0010-7824

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To determine whether phosphodiesterase (PDE) 3 inhibitors prevent the  
 resumption of meiosis by primate oocytes in vivo, rhesus macaques were  
 stimulated to develop multiple preovulatory follicles by administering  
 human recombinant gonadotropins, and follicles were aspirated 34 h  
 after an **ovulatory** stimulus (human **chorionic**  
**gonadotropin [hCG]**). Monkeys received no further  
 treatment (controls) or the PDE3 inhibitor ORG 9935 (a) exclusively in  
 the periovulatory interval beginning 6-12 h prior to receiving  
**hCG** at 200 mg/kg every 12 h orally (PER200) or a 200 mg/kg  
 oral loading dose followed by 50 mg/kg s.c. every 6 h (PER50) or (b)  
 throughout the **ovarian stimulation** protocol with  
 daily increases until a dose of 200 mg/kg bid was administered onward  
 from the eighth day of **ovarian stimulation**

(EXT200). The primary outcome was the number of oocytes that had resumed meiosis (germinal vesicle breakdown [GVBD]) at collection. At initial aspiration, 85% of oocytes recovered from control animals (n=4) had progressed to GVBD compared with 53% (p<.01), 23% (p<.01), and 13% (p<.01) recovered from animals in the PER200 (n=2), PER50 (n=1) and EXT200 (n=3) groups, resp. Although spontaneous maturation of oocytes was observed during follow-up culture in the absence of ORG 9935, none of the oocytes in the PER50 or EXT200 underwent normal **fertilization** in vitro. These results demonstrate that the PDE3 inhibitor ORG 9935 blocks oocyte maturation during gonadotropin-stimulated ovarian cycles in rhesus macaques and suggest that PDE3 inhibitors have potential clin. use as contraceptives in women.

IT 9002-61-3, Human chorionic gonadotropin

9036-21-9, Phosphodiesterase 3

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(phosphodiesterase 3 inhibitor ORG 9935 inhibits oocyte maturation during gonadotropin-stimulated ovarian cycles  
in rhesus macaques in relation to use as contraceptive)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR  
THIS RECORD. ALL CITATIONS AVAILABLE IN THE  
RE FORMAT

L56 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 30 Dec 2004

ACCESSION NUMBER: 2004:1155578 HCAPLUS

DOCUMENT NUMBER: 142:107087

TITLE: Pharmacological inhibition of  
**phosphodiesterase 4** triggers  
**ovulation** in follicle-  
**stimulating hormone**-primed rats

AUTHOR(S): McKenna, Sean D.; Pietropaolo, Michael; Tos,  
Enrico Gillio; Clark, Ann; Fischer, David; Kagan,  
David; Bao, Bagna; Chedrese, P. Jorge; Palmer,  
Stephen

CORPORATE SOURCE: Serono Reproductive Biology Institute, Rockland,  
MA, 02370, USA

SOURCE: Endocrinology (2005), 146(1), 208-214

CODEN: ENDOAO; ISSN: 0013-7227

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Phosphodiesterases (PDEs) are a family of enzymes that hydrolyze cyclic nucleotides to render them biol. inactive. As such, these enzymes are critical regulators of signal transduction pathways that use cyclic nucleotides as second messengers. **PDE4** is one such member that has been identified in ovarian tissue and purported to have a role in the regulation of gonadotropin action. In the present study, selective **PDE4** inhibitors enhanced intracellular signaling in a human **LH** receptor-expressing granulosa cell line. In vivo, **PDE4** inhibition in **FSH**-primed rats resulted in **ovulation**, indicating that the **PDE4** inhibitors can substitute for **LH** and human chorionic gonadotropin (**hCG**) in this process. Moreover, when coadministered with a subeffective dose of **hCG**, **PDE4** inhibitors acted synergistically to enhance the **ovulation** response. Inhibitors of **PDE3** or **PDE5** had no **ovulatory** effect under similar conditions. Oocytes that were **ovulated** after **PDE4** inhibition could be fertilized

10/817312

in vitro at a rate similar to that of oocytes from hCG-induced ovulation. Moreover, such oocytes were fully capable of being fertilized in vivo and developing into normal live pups. These results indicate that small mol. PDE4 inhibitors may be orally active alternatives to hCG as part of a fertility treatment regimen.

IT 9036-21-9, Phosphodiesterase 4

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; pharmacol. inhibition of phosphodiesterase 4 triggers ovulation in FSH-primed rats)

IT 9002-61-3, Human chorionic gonadotropin

9002-68-0, Follicle-stimulating

hormone 144035-83-6, Piclamilast

189940-24-7, Mesopram

RL: PAC (Pharmacological activity); BIOL (Biological study)

(pharmacol. inhibition of phosphodiesterase 4

triggers ovulation in FSH-primed rats)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 18 Oct 2004

ACCESSION NUMBER: 2004:857442 HCAPLUS

DOCUMENT NUMBER: 141:326191

TITLE: Methods for the treatment of infertility with inhibitors of phosphodiesterases (PDE) in conjunction with gonadotropins

INVENTOR(S): Palmer, Stephen S.; Mckenna, Sean D.; Arkinstall, Stephen J.; Eshkol, Aliza; Macnamee, Michael C.

PATENT ASSIGNEE(S): Applied Research Systems Ars Holding N.V., Neth. Antilles

SOURCE: PCT Int. Appl., 89 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087211	A2	20041014	WO 2004-US10346	20040401
WO 2004087211	A3	20041216		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004259792	A1	20041223	US 2004-817312	20040401
PRIORITY APPLN. INFO.:			US 2003-458955P	P 20030401

US 2003-470434P P 20030515  
 US 2004-540301P P 20040128  
 US 2004-544003P P 20040212

- AB The present invention is directed to methods of increasing oocyte production in a mammal. More specifically, the specification describes methods and compns. for inducing follicular maturation using a PDE inhibitor. The inhibitor may be used alone at high doses. Alternatively, the follicular maturation is achieved by combining a low dose of FSH with the PDE inhibitor treatment.
- IT 9002-61-3, Chorionic gonadotropin  
 9002-67-9, LH 9002-68-0, FSH  
 9002-68-0D, FSH, recombinant, urinary and human  
 9034-40-6, GnRH 9034-40-6D, GnRH, analog  
 112809-51-5, Letrozole 120511-73-1, Anastrozole 129731-10-8, Vorozole  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (combined with PDE inhibitor treatment; methods for the treatment of infertility with inhibitors of phosphodiesterases (PDE) in conjunction with gonadotropins)
- IT 9036-21-9, Phosphodiesterase 4  
 9040-59-9, 3',5'-Cyclic nucleotide phosphodiesterase  
 9068-52-4, Phosphodiesterase 5  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (inhibitors; methods for the treatment of infertility with inhibitors of phosphodiesterases (PDE) in conjunction with gonadotropins)
- IT 58-32-2, Dipyridamole 37762-06-4, Zaprinst 42971-09-5, Vinpocetine  
 66327-51-3, Furazlocillin 131774-53-3, KS-505a 136145-07-8, Arofylline  
 139755-83-2, Sildenafil 141184-34-1, Filaminast 144035-83-6, Piclamilast  
 147676-63-9 150452-19-0 153259-65-5, Ariflo 162401-32-3, Roflumilast  
 167298-74-0, SCH-51866 170632-47-0, YC-1 171596-29-5, Tadalafil  
 178308-66-2, E-4010 189940-24-7, Mesopram 191982-35-1 191982-52-2  
 215297-27-1, UK 343664 224157-99-7, Sch 59498 224785-90-4, Vardenafil 247568-68-9, FR226807  
 257892-34-5, D4418 319427-14-0, Bay-38-9456 334826-98-1,  
 5-[2-Ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)pyridin-3-yl]-3-ethyl-2-(2-methoxyethyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 335077-70-8,  
 5-(5-Acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 415916-46-0, Pharmaprojects  
 4516 415916-47-1, Pharmaprojects  
 5051 415916-49-3, Pharmaprojects  
 5064 415916-50-6, Pharmaprojects  
 5069 415916-57-3, E-8010

415916-78-8, Bay-38-3045  
 771524-82-4 773146-33-1, AWD 12-  
 171 773146-41-1, AWD 12-  
 217 773146-42-2, BMS 341400  
 773146-52-4, 5E3623 773146-54-6,  
 5E3569 773146-55-7, 5E3657  
 773146-78-4, Win 61691 773146-91-1  
 , CL 1044

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (methods for the treatment of infertility with inhibitors of  
 phosphodiesterases (PDE) in conjunction with gonadotropins)

L56 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 15 Jul 2004

ACCESSION NUMBER: 2004:565101 HCAPLUS

DOCUMENT NUMBER: 141:82340

TITLE: Use of gonadotropin releasing hormone (GnRH)  
 agonists to support the luteal phase during  
**infertility** treatment

INVENTOR(S): Loumaye, Ernest

PATENT ASSIGNEE(S): Fr.

SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058269	A1	20040715	WO 2003-IB6205	20031229
WO 2004058269	C2	20040923		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
FR 2849380	A1	20040702	FR 2002-16810	20021227
PRIORITY APPLN. INFO.:			FR 2002-16810	A 20021227
			US 2003-448468P	P 20030221

AB The invention discloses the use of an agonist of an hypothalamic hormone for the preparation of a pharmaceutical agent to support the luteal phase during **infertility** treatment of **female** mammals and more specifically of women. The pharmaceutical agent is suitable to be used for supporting the luteal phase after a spontaneous **ovulation** or after **stimulation** of **follicular** growth, trigger of final **follicular** maturation and **ovulation** with one or several addnl. agents.

IT 9034-40-6, GnRH



- RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (gonadotropin releasing hormone (GnRH) agonists to support the luteal phase during **infertility** treatment)
- IT 9002-61-3D, Chorionic gonadotrophin, analogs  
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (gonadotropin releasing hormone (GnRH) agonists to support the luteal phase during **infertility** treatment)
- IT 9002-61-3, Chorionic gonadotrophin 9002-67-9, Luteinizing hormone 9002-68-0, FSH 9002-68-0D, FSH, analogs 53714-56-0, Leuporelin 53714-56-0D, Leuporelin, analogs 57773-63-4, Triptorelin 57773-63-4D, Triptorelin, analogs 57773-65-6, Deslorelin 57773-65-6D, Deslorelin, analogs 57982-77-1, Buserelin 57982-77-1D, Buserelin, analogs 65807-02-5, Goserelin 65807-02-5D, Goserelin, analogs 76712-82-8, Histrelin 76712-82-8D, Histrelin, analogs 76932-56-4, Nafarelin 76932-56-4D, Nafarelin, analogs 112809-51-5, Letrozole 120511-73-1, **Anastrozole**  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (gonadotropin releasing hormone (GnRH) agonists to support the luteal phase during **infertility** treatment)
- IT 9025-82-5, Phosphodiesterase  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; gonadotropin releasing hormone (GnRH) agonists to support the luteal phase during **infertility** treatment)

L56 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 02 Jul 2004

ACCESSION NUMBER: 2004:529220 HCAPLUS

DOCUMENT NUMBER: 141:65113

TITLE: GnRH agonist in the treatment of **female sterility**

INVENTOR(S): Loumaye, Ernest

PATENT ASSIGNEE(S): Fr.

SOURCE: Fr. Demande, 30 pp.

CODEN: FRXXBL

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2849380	A1	20040702	FR 2002-16810	20021227
WO 2004058269	A1	20040715	WO 2003-IB6205	20031229
WO 2004058269	C2	20040923		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM,			

10/817312

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE,  
DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,  
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

FR 2002-16810

A 20021227

US 2003-448468P

P 20030221

AB The invention discloses the use of a agonist of a hypothalamic hormone in the preparation of a pharmaceutical agent for the support of the luteal phase during the treatment of **sterility** in a **female** mammal, especially a woman. The agent is adapted to use for the support of the luteal phase after a spontaneous **ovulation** or **stimulation** of the phases of **follicular** growth, final maturation of the follicles and **ovulation** by one or more therapeutic agents.

IT 9034-40-6, GnRH

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (GnRH agonist in the treatment of **sterility**)

IT 9002-61-3, Chorionic gonadotropin

9002-61-3D, Chorionic gonadotropin, analogs 9002-67-9, LH 9002-67-9D, Luteinizing hormone, analogs 9002-68-0, Follicle-stimulating hormone

9002-68-0D, Follicle-stimulating hormone, derivs. 53714-56-0, Leuprorelin 57773-63-4, Triptorelin 57982-77-1, Buserelin 65807-02-5, Goserelin 76932-56-4, Nafarelin 112809-51-5, Letrozole 120511-73-1, Anastrozole

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (GnRH agonist in the treatment of **sterility**)

IT 9025-82-5, Phosphodiesterase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; GnRH agonist in the treatment of **sterility**)

REFERENCE COUNT:

6

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 15 Apr 2004

ACCESSION NUMBER: 2004:308436 HCAPLUS

DOCUMENT NUMBER: 140:339340

TITLE: Preparation of piperazine derivatives for the treatment of mammalian infertility

INVENTOR(S): Magar, Sharad; Goutopoulos, Andreas; Liao, Yihua; Schwarz, Matthias; Russell, Thomas J.

PATENT ASSIGNEE(S): Applied Research Systems Ars Holding N.V., Neth. Antilles

SOURCE: PCT Int. Appl., 62 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.

KIND

DATE

APPLICATION NO.

DATE

Searcher : Shears 571-272-2528

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WO 2004031182	A1	20040415	WO 2003-EP50640	20030919
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,				
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB,				
GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,				
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,				
MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,				
SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,				
YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,				
BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,				
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,				
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,				
NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

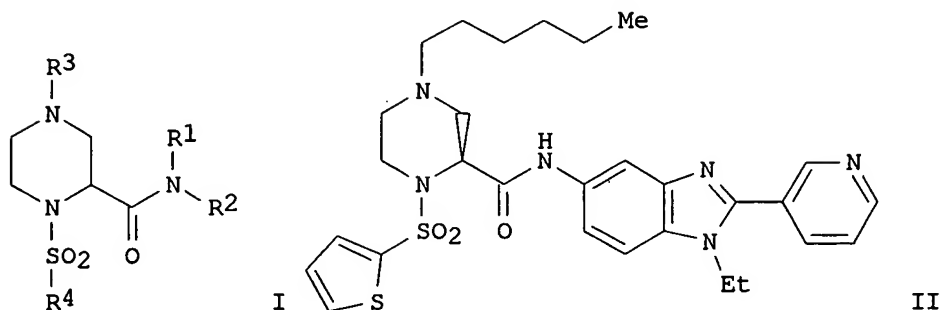
US 2002-412308P

P 20020920

OTHER SOURCE(S):

MARPAT 140:339340

GI



AB The invention provides piperazine-2-carboxamides I [R1, R2 = H, alkyl, aryl, etc.; R3 = alkyl, alkenyl, aryl, etc.; R4 = alkyl, alkenyl, aryl] that are potent FSH receptor (FSH) agonists. E.g., a 5-step synthesis of the carboxamide II, starting from (2R)-piperazine-2-carboxylic acid.2HCl, which showed ED50 of 40 nM in FSH assay, was given. The pharmaceutical composition comprising the compound I is claimed.

IT 9036-21-9, PDE4

RL: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of piperazine-2-carboxamides for the treatment of a subject suffering from disease associated with phosphodiesterase PDE4, adenosine transporters, or prostanoid receptors)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 04 Jan 2004

ACCESSION NUMBER: 2004:3645 HCAPLUS

DOCUMENT NUMBER: 140:36390

TITLE: Enhancement of endogenous gonadotropin and androgen production with GnRH agonists

INVENTOR(S): Taneja, Rajneesh

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 5 pp.

10/817312

DOCUMENT TYPE: CODEN: USXXCO  
LANGUAGE: Patent  
FAMILY ACC. NUM. COUNT: 1 English  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004002445	A1	20040101	US 2003-397076	20030326
PRIORITY APPLN. INFO.:			US 2002-319158P	P 20020328

AB Provided herein is a method of enhancing endogenous gonadotropin and androgen production comprising administering a therapeutically effective amount of at least one GnRH agonist to a patient in need of such treatment. Phosphodiesterase inhibitors and dopamine agonists can further be administered with the GnRH agonist. Increasing gonadotropin and androgen production is effective for the treatment of hypogonadism, cryptorchidism, amenorrhea, erectile dysfunction and fertility disorders.

IT 9034-40-6, GnRH  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(agonist; enhancement of endogenous gonadotropin and androgen production and treatment of disorders related to low production with GnRH agonists)

IT 74381-53-6, Leuprolide acetate  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(enhancement of endogenous gonadotropin and androgen production and treatment of disorders related to low production with GnRH agonists)

IT 9025-82-5, Phosphodiesterase  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(inhibitor, co-administered with GnRH agonist; enhancement of endogenous gonadotropin and androgen production and treatment of disorders related to low production with GnRH agonists)

L56 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 03 Oct 2003

ACCESSION NUMBER: 2003:777372 HCAPLUS

DOCUMENT NUMBER: 139:255773

TITLE: Enhancement of endogenous gonadotropin production

INVENTOR(S): Taneja, Rajneesh

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 5 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003186892	A1	20031002	US 2002-63197	20020328
CA 2480626	AA	20031009	CA 2003-2480626	20030131
WO 2003082319	A1	20031009	WO 2003-US3131	20030131

W: CA, JP, MX

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, SE, SI, SK, TR

Searcher : Shears 571-272-2528

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EP 1490091      A1      20041229      EP 2003-706050      20030131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, FI, CY, TR, BG, CZ, EE, HU, SK
PRIORITY APPLN. INFO.: US 2002-63197      A      20020328
WO 2003-US3131      W      20030131
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AB    Provided herein is a method of enhancing endogenous gonadotropin and androgen production comprising administering a therapeutically effective amount of at least one GnRH agonist to a patient in need of such treatment.

IT 9034-40-6, Gonadotropin releasing hormone  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(enhancement of endogenous gonadotropin production)

IT 74381-53-6, Lupron  
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(enhancement of endogenous gonadotropin production)

IT 9025-82-5, Phosphodiesterase  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitor; enhancement of endogenous gonadotropin production)

L56 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN  
ED Entered STN: 09 Jun 2003

ACCESSION NUMBER: 2003:438545 HCAPLUS

DOCUMENT NUMBER: 139:224722

**TITLE:** Phosphodiesterase regulation is critical for the differentiation and pattern of gene expression in granulosa cells of the ovarian follicle

AUTHOR(S): Park, Jy-Young; Richard, Francois; Chun, Sang-Young; Park, Jeong-Hoh; Law, Evelyn; Horner, Kathleen; Jin, S.-L. Catherine; Conti, Marco

CORPORATE SOURCE: Division of Reproductive Biology, Department of Obstetrics and Gynecology, Stanford University, Stanford, CA, 94305, USA

SOURCE: Molecular Endocrinology (2003), 17(6), 1117-1130  
CODEN: MOENEN; ISSN: 0888-8809

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Feedback regulations are integral components of the cAMP signaling required for most cellular processes, including gene expression and cell differentiation. Here, the authors provide evidence that one of these feedback regulations involving the cyclic nucleotide phosphodiesterase PDE4D plays a critical role in cAMP signaling during the differentiation of granulosa cells of the ovarian follicle. Gonadotropins induce PDE4D mRNA and increase the cAMP hydrolyzing activity in granulosa cells, demonstrating that a feedback regulation of cAMP is operating in granulosa cells *in vivo*. Inactivation of the PDE4D by homologous recombination is associated with an altered pattern of cAMP accumulation induced by the gonadotropin LH/human chorionic gonadotropin (hCG), impaired female fertility, and a markedly decreased ovulation rate. In spite of a disruption of the cAMP response, LH/hCG induced P 450 side chain cleavage expression and steroidogenesis in a manner similar to wild-type controls. Morphol. examination of the ovary of PDE4D<sup>-/-</sup> mice indicated luteinization of antral follicles with entrapped oocytes. Consistent

with the morphol. finding of unruptured follicles, LH/hCG induction of genes involved in ovulation, including cyclooxygenase-2, progesterone receptor, and the downstream genes, is markedly decreased in the PDE4D-/- ovaries. These data demonstrate that PDE4D regulation plays a critical role in gonadotropin mechanism of action and suggest that the intensity and duration of the cAMP signal defines the pattern of gene expression during the differentiation of granulosa cells.

IT 9036-21-9, Cyclic nucleotide phosphodiesterase

4

RL: BSU (Biological study, unclassified); BIOL (Biological study) (isoform 4D; phosphodiesterase regulation is critical for differentiation and pattern of gene expression in granulosa cells of ovarian follicle as studied in mouse and rat)

IT 9002-61-3, Chorionic gonadotropin

9002-67-9, LH 9002-68-0, FSH

RL: BSU (Biological study, unclassified); BIOL (Biological study) (phosphodiesterase regulation is critical for differentiation and pattern of gene expression in granulosa cells of ovarian follicle as studied in mouse and rat)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 09 Jan 2003

ACCESSION NUMBER: 2003:18995 HCAPLUS

DOCUMENT NUMBER: 138:265895

TITLE: Phosphodiesterase expression targeted to gonadotropin-releasing hormone neurons inhibits luteinizing hormone pulses in transgenic rats

AUTHOR(S): Paruthiyil, Sreenivasan; El Majdoubi, Mohammed; Conti, Marco; Weiner, Richard I.

CORPORATE SOURCE: Department of Obstetrics, Gynecology, University of California, San Francisco, CA, 94143, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(26), 17191-17196

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Expts. in the GT1 gonadotropin-releasing hormone (GnRH) cell line have shown that the cAMP signaling pathway plays a central role in regulating the excitability of the cells. Lowering cAMP levels by expressing the constitutively active cAMP-specific phosphodiesterase PDE4D1 in GT1 cells inhibited spontaneous Ca<sup>2+</sup> oscillations and intrinsic pulsatile GnRH secretion. To address the role of cAMP levels in endogenous GnRH neurons, the authors genetically targeted expression of PDE4D1 (P) to GnRH neurons in transgenic rats (R) by using the GnRH gene promoter/enhancer regions (G). Three lines of transgenic rats, GPR-2, -4, and -5, were established. In situ hybridization and RT-PCR studies demonstrated that transgene expression was specifically targeted to GnRH neurons. Decreased fertility was observed in female but not in male rats from all three lines. The mean LH levels in ovariectomized rats were significantly reduced in the GPR-4 and -5 lines but not in the GPR-2 line. In castrated male and female GPR-4 rats,

the LH pulse frequency was dramatically reduced. Six of twelve GPR-4 females studied did not ovulate and had polycystic ovaries. The remaining six females ovulated, but the magnitude of the preovulatory LH surge was inhibited by 63%. These findings support the hypothesis that cAMP signaling may play a central role in regulating excitability of GnRH neurons in vivo. The GPR-4 line of transgenic rats provides a genetic model for the understanding of the role of pulsatile gonadotropin release in follicular development.

IT 9036-21-9, CAMP-specific Phosphodiesterase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (PDE4D1; phosphodiesterase expression targeted to LH-RH neurons effect on LH pulses and reproductive function in transgenic rats)

IT 9002-67-9, LH 9002-68-0, FSH  
9034-40-6, LH-RH

RL: BSU (Biological study, unclassified); BIOL (Biological study) (phosphodiesterase expression targeted to LH-RH neurons effect on LH pulses and reproductive function in transgenic rats)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 10 Dec 2002

ACCESSION NUMBER: 2002:937303 HCAPLUS

DOCUMENT NUMBER: 138:20443

TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes

INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin

PATENT ASSIGNEE(S): Takara Bio Inc., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A 20010314
			JP 2001-74993	A 20010315
			JP 2001-102519	A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes

whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17- $\beta$  estradiol (E2), were found in mice by DNA chip anal.

- IT **9036-21-9**, CAMP-specific phosphodiesterase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (cAMP-specific phosphodiesterase (Pde4b); endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes)
- IT **9040-59-9, Phosphodiesterase 1**  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes)
- IT **9034-40-6, LRF**  
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (leukemia/lymphoma related factor LRF; endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes)

L56 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 02 Aug 2002

ACCESSION NUMBER: 2002:575737 HCAPLUS

DOCUMENT NUMBER: 137:135500

TITLE: Methods of inducing **ovulation** by administering a non-polypeptide cAMP level modulator

INVENTOR(S): Palmer, Stephen; McKenna, Sean; Tepper, Mark; Eshkol, Aliza; MacNamee, Michael C.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 26 pp., Cont.-in-part of U.S. Ser. No. 928,268.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002103106	A1	20020801	US 2001-14812	20011214
US 2002065324	A1	20020530	US 2001-928268	20010810
EP 1463493	A1	20041006	EP 2001-274987	20011214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001017198	A	20041026	BR 2001-17198	20011214
PRIORITY APPLN. INFO.:			US 2000-224962P	P 20000811
			US 2001-928268	A2 20010810
			WO 2001-EP14730	W 20011214

AB The present invention relates to methods of inducing **ovulation** in a **female** host comprising the administration of a non-polypeptide cAMP level modulator to the **female** host. In another aspect, the invention provides for specific administration of the phosphodiesterase inhibitor prior to the luteal phase of the host's **ovulatory** cycle. Preferred non-polypeptide cAMP level modulator include phosphodiesterase inhibitors, particularly inhibitors of **phosphodiesterase 4** isoforms. Pharmaceutical compns. containing the cAMP modulators are also claimed.



- IT 9036-21-9  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(IV, inhibitors; methods of inducing **ovulation** by  
administering a non-polypeptide cAMP level modulator)
- IT 141184-34-1, PDA 641  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(PDA 641; methods of inducing **ovulation** by administering  
a non-polypeptide cAMP level modulator)
- IT 37762-06-4, Zaprinas 42971-09-5,  
Vinpocetine 136145-07-8, Arofylline  
144035-83-6 147676-63-9, GF-248 150452-19-0  
, E-4021 153259-65-5 162401-32-3,  
Roflumilast 257892-34-5, D 4418  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(methods of inducing **ovulation** by administering a  
non-polypeptide cAMP level modulator)
- IT 9002-67-9, LH  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(methods of inducing **ovulation** by administering a  
non-polypeptide cAMP level modulator in combination with **LH**  
)
- IT 9002-61-3, Chorionic gonadotropin  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(methods of inducing **ovulation** by administering a  
non-polypeptide cAMP level modulator in combination with  
**chorionic gonadotropin**)
- IT 9002-68-0, FSH  
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
(Biological study); USES (Uses)  
(methods of **stimulating follicular** development  
and inducing **ovulation** by administering an agent that  
increases **FSH** along with a cAMP level modulator)

L56 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 31 May 2002

ACCESSION NUMBER: 2002:409272 HCAPLUS

DOCUMENT NUMBER: 136:396388

TITLE: Methods of **stimulating**  
**follicular** development and inducing  
**ovulation** with a non-polypeptide cAMP  
level modulator and an agent that increases  
**FSH** concentration

INVENTOR(S): Palmer, Stephen; McKenna, Sean; Tepper, Mark;  
Eshkol, Aliza; Macnamee, Michael C.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 20 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002065324	A1	20020530	US 2001-928268	20010810

US 2002103106 A1 20020801 US 2001-14812 20011214  
 WO 2003051344 A1 20030626 WO 2001-EP14730 20011214  
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,  
 CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,  
 GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,  
 LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
 NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
 TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,  
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI,  
 FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG,  
 CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 EP 1463493 A1 20041006 EP 2001-274987 20011214  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,  
 PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR  
 BR 2001017198 A 20041026 BR 2001-17198 20011214  
 PRIORITY APPLN. INFO.: US 2000-224962P P 20000811  
 US 2001-928268 A2 20010810  
 WO 2001-EP14730 W 20011214

AB The present invention relates to methods of inducing **ovulation** in a **female** host comprising the administration of a non-polypeptide cAMP level modulator to the **female** host. In another aspect, the invention provides for specific administration of the phosphodiesterase inhibitor prior to the luteal phase of the host's **ovulatory** cycle. Preferred non-polypeptide cAMP level modulator include phosphodiesterase inhibitors, particularly inhibitors of **phosphodiesterase 4** isoforms. A method of a combined treatment for **stimulating follicular** development and **ovulation** induction in a **female** host comprising the administration of an agent which increases **FSH** concns. in said host during the **follicular** phase of the host's **ovulatory** cycle and administering a nonpolypeptide cAMP level modulator to said host prior to the luteal phase of the host 's **ovulatory** cycle.

IT 9036-21-9

RL: BSU (Biological study, unclassified); BIOL (Biological study) (IV, inhibitors as cAMP level modulators; methods of **stimulating follicular** development and inducing **ovulation** with a non-polypeptide cAMP level modulator and an agent that increases **FSH** concentration)

IT 9025-82-5, Phosphodiesterase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors as cAMP level modulators; methods of **stimulating follicular** development and inducing **ovulation** with a non-polypeptide cAMP level modulator and an agent that increases **FSH** concentration)

IT 9002-68-0, Follicle stimulating

hormone

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (methods of **stimulating follicular** development and inducing **ovulation** with a non-polypeptide cAMP level modulator and an agent that increases **FSH** concentration)

IT 9002-61-3, Chorionic gonadotropin

9002-67-9, Luteinizing hormone

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)  
 (methods of **stimulating follicular** development  
 and inducing **ovulation** with a non-polypeptide cAMP level  
 modulator and an agent that increases **FSH** concentration)

L56 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 10 Apr 2002

ACCESSION NUMBER: 2002:268325 HCAPLUS

DOCUMENT NUMBER: 137:137933

TITLE: Differential Effects of Specific Phosphodiesterase  
 Isoenzyme Inhibitors on Bovine Oocyte Meiotic  
 Maturation

AUTHOR(S): Thomas, Rebecca E.; Armstrong, David T.;  
 Gilchrist, Robert B.

CORPORATE SOURCE: Reproductive Medicine Unit, Department of  
 Obstetrics and Gynaecology, The University of  
 Adelaide, The Queen Elizabeth Hospital, Adelaide,  
 5011, Australia

SOURCE: Developmental Biology (Orlando, FL, United States)  
 (2002), 244(2), 215-225

CODEN: DEBIAO; ISSN: 0012-1606

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The differential regulation of cAMP levels within the oocyte and somatic (cumulus) cell compartments of the bovine follicle, and the subsequent regulation of oocyte meiotic maturation was examined through specific cell-type localization of phosphodiesterases (PDEs). Selective PDE inhibitors were used to modulate cAMP levels in each of the two follicular compartments and to examine their effects on oocyte meiotic maturation. Ovaries were obtained from an abattoir and cumulus-oocyte complexes (COC) were aspirated from antral follicles into culture medium supplemented with 4 mg/mL BSA and 2 mM 3-isobutyl-1-methylxanthine (IBMX). COC, denuded oocytes (DO), or mural granulosa cells (MGC) were cultured either with or without forskolin or **FSH**, in the presence of specific PDE inhibitors; either milrinone (PDE3 inhibitor), cilostamide (PDE3 inhibitor), or rolipram (PDE4 inhibitor). COC/DO cultures were assessed for meiotic progression and cAMP content, and MGC for cAMP production. The type 3 PDE inhibitor, but not the type 4, prevented spontaneous meiotic maturation and elevated intraoocyte cAMP in cultured denuded oocytes. In contrast, the type 4 PDE inhibitor had no effect on the **oocyte**, but elevated mural granulosa and cumulus cell cAMP **production**. The results of this study indicate that specific PDE subtypes are differentially localized within the two compartments of the bovine follicle-the type 3 PDE in the oocyte and the type 4 PDE in the granulosa cells. In addition, oocyte cAMP levels are primarily regulated in bovine oocytes by its degradation by PDE, whereas granulosa cell cAMP levels are controlled mainly by active adenylate cyclase, with both sources able to participate in oocyte meiotic regulation.

IT 9036-21-9, Adenosine cyclic 3',5'-phosphate phosphodiesterase  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (isoenzyme 3, 4; roles of specific cyclic nucleotide  
 phosphodiesterase isoenzymes on bovine oocyte meiotic maturation)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR  
 THIS RECORD. ALL CITATIONS AVAILABLE IN THE  
 RE FORMAT

L56 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 28 Oct 1999

ACCESSION NUMBER: 1999:685028 HCAPLUS

DOCUMENT NUMBER: 132:21851

TITLE: Impaired growth and **fertility** of  
cAMP-specific phosphodiesterase PDE4D-deficient  
miceAUTHOR(S): Jin, S.-L. Catherine; Richard, Francois J.; Kuo,  
Wie-Peng; D'Ercole, A. Joseph; Conti, MarcoCORPORATE SOURCE: Division of Reproductive Biology, Department of  
Gynecology and Obstetrics, Stanford University  
School of Medicine, Stanford, CA, 94305-5317, USA  
SOURCE: Proceedings of the National Academy of Sciences of  
the United States of America (1999), 96(21),  
11998-12003

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In eukaryotic cells, the inactivation of the cyclic nucleotide signal depends on a complex array of cyclic nucleotide phosphodiesterases (PDEs). Although it has been established that multiple PDE isoenzymes with distinct catalytic properties and regulations coexist in the same cell, the physiol. significance of this remarkable complexity is poorly understood. To examine the role of a PDE in cAMP signaling in vivo, we have inactivated the type 4 cAMP-specific PDE (PDE4D) gene, a mammalian homolog of the *Drosophila dunce*. This isoenzyme is involved in feedback regulation of cAMP levels. Mice deficient in PDE4D exhibit delayed growth as well as reduced viability and **female fertility**. The decrease in **fertility** of the null **female** is caused by impaired ovulation and diminished sensitivity of the granulosa cells to gonadotropins. These pleiotropic phenotypes demonstrate that PDE4D plays a critical role in cAMP signaling and that the activity of this isoenzyme is required for the regulation of growth and **fertility**.

IT 9002-61-3, Human chorionic gonadotropin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study) (diminished sensitivity of granulosa cells to gonadotropins in cAMP-specific phosphodiesterase type 4-deficient mice)

IT 9036-21-9, CAMP-specific phosphodiesterase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (type 4; impaired growth and **fertility** of cAMP-specific phosphodiesterase PDE4D-deficient mice)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L56 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 11 Jan 1997

ACCESSION NUMBER: 1997:17398 HCAPLUS

DOCUMENT NUMBER: 126:129758

TITLE: Src tyrosine kinase activity in rat  
thecal-interstitial cells and mouse TM3 Leydig  
cells is positively associated with cAMP-specific  
phosphodiesterase activityAUTHOR(S): Taylor, Christopher C.; Limback, Darlene;  
Terranova, Paul F.

CORPORATE SOURCE: Department of Physiology, Center for Reproductive

Sciences, University of Kansas Medical Center,  
 Kansas City, KS, 66160-7401, USA  
 SOURCE: Molecular and Cellular Endocrinology (1997),  
 126(1), 91-100  
 CODEN: MCEND6; ISSN: 0303-7207  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Phosphodiesterases (PDEs) play a critical role in the regulation of  
 intracellular cyclic nucleotide concentration and, consequently, regulate  
 the

state of cellular differentiation. We have reported that the  
 Src-selective tyrosine kinase inhibitor, herbimycin A, potentiates  
**LH-stimulated** cAMP accumulation in culture media by  
**ovarian** thecal-interstitial cells (TIC; see Taylor, C. and  
 Terranova, P.F. (1995) Lipopolysaccharide inhibits rat **ovarian**  
 thecal-interstitial cell steroid secretion in vitro. Endocrinol. 136,  
 5527-5532). The present study was conducted to investigate the  
 effects of herbimycin, and changes in Src tyrosine kinase activity, on  
 PDE activity in rat TIC and in the mouse TM3 Leydig cell line.  
 Treatment of TIC with herbimycin (1  $\mu$ M) for 24 h inhibited basal  
 and LH-stimulated PDE activity (.apprx.50 and 70%, resp.)  
 and was associated with an increase in cAMP and progesterone accumulation  
 in culture media. Treatment of TM3 cells with herbimycin inhibited  
 PDE activity and increased cAMP accumulation in a dose- and  
 time-dependent manner. TM3 cell cultures challenged with herbimycin  
 had lower Src tyrosine kinase activity than controls (.apprx.50%);  
 however, protein kinase A activity was unaffected. TM3 cells stably  
 transfected with a dominant neg. Src tyrosine kinase (TM3Src<sup>-</sup>) had  
 lower PDE activity than cells transfected with a G418 resistance gene  
 alone (TM3pSV2neo) which served as control cells. Conversely, TM3  
 cells expressing a temperature-sensitive Src kinase had significantly  
 greater PDE activity at the Src active temperature (35°; the temperature at  
 which the enzyme is active) than TM3pSV2neo control cells grown at the  
 same temperature TM3 cell lysates hydrolyzed minimal amts. of cGMP,  
 indicating a cAMP-specific PDE. Phosphodiesterase activity in both  
 TM3 and rat TIC was sensitive to the PDE4-selective  
 inhibitor RO20-1724, indicating the predominant active enzyme is  
 probably a member of the cAMP-specific PDE4 family. From  
 the present data, we conclude that a tyrosine kinase of the Src family  
 may play an important role in regulating phosphodiesterase activity in  
 thecal and Leydig cells, and thus regulate intracellular cAMP and the  
 state of cellular differentiation.

IT 9036-21-9, CAMP-specific phosphodiesterase

RL: BAC (Biological activity or effector, except adverse); BPR  
 (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)

(Src tyrosine kinase activity in rat thecal-interstitial cells and  
 mouse TM3 Leydig cells is pos. associated with cAMP-specific  
 phosphodiesterase activity)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR  
 THIS RECORD. ALL CITATIONS AVAILABLE IN THE  
 RE FORMAT

L56 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 02 Oct 1996

ACCESSION NUMBER: 1996:584703 HCAPLUS

DOCUMENT NUMBER: 125:293471

TITLE: Oocyte maturation involves compartmentalization

and opposing changes of cAMP levels in follicular somatic and germ cells: studies using selective phosphodiesterase inhibitors

AUTHOR(S): Tsafiriri, A.; Chun, Sang-Young; Zhang, Ruobo; Hsueh, A. J. W.; Conti, M.

CORPORATE SOURCE: Dep. Obstetrics and Gynecology, Stanford Univ. School Medicine, Stanford, CA, 94305-5317, USA

SOURCE: Developmental Biology (1996), 178(2), 393-402  
CODEN: DEBIAO; ISSN: 0012-1606

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The second messenger cAMP has been implicated in the regulation of mammalian and amphibian oocyte maturation. Although a decrease in intra-oocyte levels of cAMP precedes germinal vesicle breakdown (GVBD), the gonadotropin induction of **ovulation** and oocyte maturation is associated with major increases of cAMP in ovarian follicles. In the mammalian system, isolated oocytes undergo spontaneous maturation in vitro but this process is blocked by treatment with a phosphodiesterase (PDE) inhibitor, IBMX, which increases intra-oocyte cAMP levels. In contrast, the same inhibitor, when added to cultured follicles for a brief time, increases follicle cAMP levels, followed by the induction of GVBD. To resolve the paradoxical actions of this PDE inhibitor on the maturation of isolated and follicle-enclosed oocytes, the authors hypothesized that meiotic maturation requires opposing fluctuations of cAMP levels in the somatic granulosa and germ cells. Such opposing fluctuations may result from selective expression and regulation of PDEs in the somatic and germ cell compartments of the follicle. To test this hypothesis, PDE activity was manipulated in different follicular cells using type-specific inhibitors. The impact of the ensuing changes in cAMP levels in the two compartments was monitored by the induction of GVBD. In isolated oocytes, spontaneous GVBD was blocked by two inhibitors of type 3 PDE (cGMP-inhibited: CGI-PDE), milrinone and cilostamide. In contrast, treatment with an inhibitor for type 4 PDE (cAMP-specific), rolipram, was ineffective. These findings suggest that the oocyte expresses type 3 but not type 4 PDE and that increases in intra-oocyte cAMP suppress GVBD. This hypothesis was confirmed by in situ hybridization studies with PDE3 and **PDE4** probes. PDE3B mRNA was concentrated in oocytes while PDE4D was mainly expressed in granulosa cells. In cultured follicles, **LH** treatment induced oocyte maturation but the gonadotropin action was blocked by inhibitors of type 3 but not the type 4 PDE inhibitors. Furthermore, treatment with the type 4, but not the type 3, PDE inhibitor mimics the action of **LH** and induces oocyte maturation, presumably by increasing cAMP levels in granulosa cells. The authors' findings indicate that PDE subtypes 4 and 3 are located in follicle somatic and germ cells, resp. Preferential inhibition of PDE 3 in the oocyte may lead to a delay in oocyte maturation without affecting the cAMP-induced **ovulatory** process in the somatic cells. Conversely, selective suppression of granulosa cell cAMP-PDE may enhance the gonadotropin induction of **ovulation** and oocyte maturation. Thus, in addition to the well-recognized differential expression and regulation of adenylate cyclase in the somatic and germ cell compartments of the follicle, the authors suggest that selective regulation and expression of PDEs may be involved in the regulation of cAMP levels and control of oocyte maturation in the preovulatory mammalian follicle.

IT 9002-67-9, **LH**

RL: BAC (Biological activity or effector, except adverse); BSU

(Biological study, unclassified); BIOL (Biological study)  
 (oocyte maturation in relation to cAMP phosphodiesterase isoform  
 compartmentalization and opposing changes of cAMP levels in  
 follicular somatic and germ cells in response to LH)

IT 9036-21-9, CAMP phosphodiesterase

RL: BOC (Biological occurrence); BPR (Biological process); BSU  
 (Biological study, unclassified); BIOL (Biological study); OCCU  
 (Occurrence); PROC (Process)

(oocyte maturation in relation to cAMP phosphodiesterase isoform  
 compartmentalization and opposing changes of cAMP levels in  
 follicular somatic and germ cells in response to LH)

L56 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 23 May 1995

ACCESSION NUMBER: 1995:566687 HCAPLUS

DOCUMENT NUMBER: 123:5984

TITLE: Bursal antisteroidogenic peptide alters the  
 activity of steroidogenic enzymes in chicken  
 granulosa cells

AUTHOR(S): Dean, C. E.; Byrd, J. A.; Hargis, B. M.

CORPORATE SOURCE: Texas Agricultural Experiment Station, Texas A and  
 M University System, College Station, TX, 77843,  
 USA

SOURCE: Domestic Animal Endocrinology (1995), 12(1), 51-61  
 CODEN: DANEEE; ISSN: 0739-7240

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have previously reported that a peptide from chicken bursa of  
 Fabricius, bursal antisteroidogenic peptide (BASP), inhibits  
**LH-stimulated** progesterone biosynthesis by chicken  
**ovarian** granulosa cells. The objective of this study was to  
 determine the site(s) of BASP inhibition within the steroidogenic pathway  
 of chicken granulosa cells. The effects of BASP on key steroidogenic  
 enzymes, including adenylyl cyclase (AC), phosphodiesterase, the  
 cholesterol side-chain cleavage enzyme complex and  
 3 $\beta$ -hydroxysteroid dehydrogenase were determined **LH** (10  
 ng/tube) stimulated a fivefold increase in granulosa cell progesterone  
 production that was inhibited by BASP (0.06, 0.12 or 0.25 bursal equivalent)  
 in a dose-dependent manner. **LH** stimulated a sixfold  
 increase in cAMP formation, and this increase was potentiated by BASP  
 in a dose-dependent manner. In addition, BASP stimulated cAMP formation  
 in the absence of **LH** without affecting progesterone production  
 The AC activator forskolin (0.1 mM) stimulated a 4.5-fold increase in  
 progesterone synthesis, which was inhibited by BASP. In the presence  
 of forskolin BASP increased cAMP formation in a dose-dependent manner.  
 A fivefold increase in progesterone synthesis induced by the  
 phosphodiesterase inhibitor IBMX (1.0 mM) was inhibited by BASP. In  
 the presence of IBMX, BASP increased cAMP formation in a  
 dose-dependent manner. Finally, 22(R)-hydroxycholesterol (250, 500,  
 1,000, or 2,500 ng/tube) or pregnenolone (50, 100, 200, or 500  
 ng/tube) resulted in up to 15- or 10-fold increases in progesterone  
 production, resp. Increasing concns. of BASP caused a dose-dependent  
 suppression of the conversion of 22(R)-hydroxycholesterol, but not  
 pregnenolone, to progesterone. The inhibition of steroidogenesis by  
 BASP is not associated with reduced cAMP levels, and BASP appears to  
 strongly stimulate AC activity. In addition, these findings suggest that  
 BASP may limit the availability of progesterone precursors by  
 inhibiting the activity of the cholesterol side-chain cleavage enzyme  
 complex.

IT 9025-82-5, Phosphodiesterase  
 RL: BPR (Biological process); BSU (Biological study, unclassified);  
 BIOL (Biological study); PROC (Process)  
 (bursal antisteroidogenic peptide alteration of steroidogenic  
 enzymes in chicken granulosa cells)

L56 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 21 Jan 1989

ACCESSION NUMBER: 1989:18726 HCAPLUS

DOCUMENT NUMBER: 110:18726

TITLE: The effects of **follicle-**  
**stimulating hormone** and cyclic  
 guanosine 3',5'-monophosphate on cyclic adenosine  
 3',5'-monophosphate-phosphodiesterase and  
 resumption of meiosis in hamster cumulus-oocyte  
 complexes

AUTHOR(S): Hubbard, C. J.; Price, J.

CORPORATE SOURCE: Dep. Biol. Sci., North Illinois Univ., DeKalb, IL,  
 60115, USA

SOURCE: Biology of Reproduction (1988), 39(4), 829-38

CODEN: BIREBV; ISSN: 0006-3363

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of **FSH** and cGMP on spontaneous oocyte maturation  
 and cAMP phosphodiesterase activity (cAMP-PDE) were evaluated by using  
 cumulus-oocyte complexes (COCs) from proestrous hamsters. After a 2-h  
 incubation period, **FSH** reduced the percentage of maturing  
 oocytes compared with controls. This inhibition was partially  
 overcome when cGMP-elevating agents (8-bromo-cGMP, atrial natriuretic  
 factor, or sodium nitroprusside) were included with **FSH**.  
 After a 3-h period, incubation with **FSH** or with  
 cGMP-elevating agents alone increased the maturation rate above that  
 of the controls. The accelerating effects of cGMP on the maturation  
 rate appear to be caused by its capacity to lower cAMP levels.  
 Combining **FSH** with sodium nitroprusside reduced cAMP levels  
 in COCs (not oocytes) compared with groups exposed to **FSH**  
 alone. **FSH** increased cGMP levels in COCs in a dose- and  
 time-dependent manner. Both **FSH** and cGMP-elevating agents  
 produced a dose-dependent increase in cAMP-PDE activity in  
 COCs (not oocytes) following a 2-h incubation period. In  
 vivo, **FSH** apparently stimulates a rise in both cAMP and cGMP  
 in COCs. Although the increase in cAMP may be the initial meiotic  
 trigger, cGMP may serve to subsequently lower cAMP by activating  
 cAMP-PDE and thus permit the maturational process to continue.

IT 9002-68-0, **FSH**

RL: BIOL (Biological study)

(cAMP phosphodiesterase of cumulus-oocyte complex response to,  
 meiosis in relation to)

IT 9036-21-9, cAMP phosphodiesterase

RL: BIOL (Biological study)

(of cumulus-oocyte complex, cGMP and **FSH** effect on,  
 meiosis in relation to)

L56 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 20 Feb 1988

ACCESSION NUMBER: 1988:49914 HCAPLUS

DOCUMENT NUMBER: 108:49914

TITLE: Adenosine receptor-mediated effects by  
 nonmetabolizable adenosine analogs in preovulatory



rat granulosa cells: a putative local regulatory role of adenosine in the ovary  
 AUTHOR(S): Billig, Haakan; Thelander, Harriet; Rosberg, Sten  
 CORPORATE SOURCE: Dep. Physiol., Univ. Goeteborg, Goeteborg, S-400 33, Swed.  
 SOURCE: Endocrinology (1988), 122(1), 52-61  
 CODEN: ENDOAO; ISSN: 0013-7227  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The influence of nonmetabolizable adenosine analogs on cAMP production was investigated in preovulatory rat granulosa cells. 5'-(N-Ethyl)carboxamido-adenosine (NECA), a stimulatory A2-adenosine receptor agonist, stimulated cAMP accumulation, and NECA and 2-chloro-adenosine also potentiated the response to FSH. The adenosine receptor antagonist 8-phenyltheophylline antagonized the effect of NECA, shown by a shift in the dose-response curve to the right. The **stimulatory** effect of NECA was also seen in an **ovarian** membrane preparation, where NECA **stimulated** adenylate cyclase in both the presence and absence of FSH. The stimulatory effect of NECA was also decreased by 8-phenyltheophylline in this preparation. The A1-receptor agonists N6-(R-phenylisopropyl)adenosine (R-PIA) and N6-(S-phenylisopropyl)adenosine (S-PIA) both inhibited FSH-stimulated cAMP accumulation. The inhibitory effects of R-PIA and S-PIA, but not the stimulatory effects of NECA, could be counteracted by **dipyridamole**, a nucleoside transport inhibitor. Furthermore, R-PIA and S-PIA inhibited adenosine uptake into granulosa cells. Thus, the inhibitory effects of R-PIA and S-PIA are not likely to be mediated via membrane-bound inhibitory A1-adenosine receptors. Neither the stimulatory effects of NECA nor the inhibitory effects of R- and S-PIA could be attributed to changes in ATP levels, since the ATP levels were unaffected by these analogs. The results indicate the existence of stimulatory A2-adenosine receptors in preovulatory rat granulosa cells and suggest a membrane-associated modulatory role of adenosine in preovulatory granulosa cells.

IT 9002-68-0, FSH  
 RL: BIOL (Biological study)  
 (cAMP accumulation by ovary granulosa cell stimulation by, adenosine and analogs effect on)

L56 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 27 Jun 1986

ACCESSION NUMBER: 1986:219788 HCAPLUS

DOCUMENT NUMBER: 104:219788

TITLE: Prostacyclin and steroidogenesis in goat ovarian cell types in vitro

AUTHOR(S): Band, Vimla; Kharbanda, S. M.; Murugesan, K.; Farooq, A.

CORPORATE SOURCE: Dep. Reprod. Biol., All-India Inst. Med. Sci., New Delhi, 110029, India

SOURCE: Prostaglandins (1986), 31(3), 509-25  
 CODEN: PRGLBA; ISSN: 0090-6980

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Granulosa, theca, and corpus luteum cells of the goat ovary were isolated and incubated sep. for 6 h, with or without various modulators. Arachidonic acid (AA) [506-32-1] (10 ng-100 µg/mL), the precursor for prostaglandin synthesis, produced a dose-dependent increase in progesterone (P4) [57-83-0] and estradiol-17β (E2)

[50-28-2] production by all the cell types. Prostaglandin synthetase inhibitors, aspirin (10-6-10-3M) and indomethacin (100 ng-1 mg/mL), produced a dose-dependent decrease in arachidonic acid-stimulated (100 µg/mL) steroid production. Prostacyclin synthetase stimulators, trapidil (1.6 µg-1 mg/mL) and **dipyridamole** (10-6-10-3M), did not affect steroid production when added alone or along with AA. Up to 100 µg/mL of U-51605 (9, 11-azoprostano-5,13-dienoic acid), a prostacyclin synthetase inhibitor, did not inhibit basal or AA-stimulated steroid production. PGI<sub>2</sub> [35121-78-9] and its stable analog 6β-PGI<sub>1</sub> [62770-50-7] (0.01-10 µg/mL) produced a dose-dependent increase in P<sub>4</sub> and E<sub>2</sub> production in all 3 cell types. 6-Keto-PGE<sub>1</sub> [67786-53-2] (an active metabolite of PGI<sub>2</sub> in certain systems) produced an increase in steroid production in theca at ≥1 µg/mL concns. but had no effect on granulosa and corpus luteum cells at any dose level. 6-Keto-PGF<sub>1α</sub> (a stable metabolite of PGI<sub>2</sub>) was without effect in the present system. The lack of effect of PGI<sub>2</sub> at lower concns. was not altered by either differentiation of the cells with **FSH** and testosterone or addition of steroid precursors, testosterone and pregnenolone. Apparently, AA-stimulated steroid production in the goat **ovarian** cell type is mediated by prostaglandins other than PGI<sub>2</sub>, though PGI<sub>2</sub> itself can pos. modulate the steroid production.

L56 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 07 Sep 1985

ACCESSION NUMBER: 1985:465341 HCAPLUS

DOCUMENT NUMBER: 103:65341

TITLE: Adenosine differentially amplifies  
luteinizing hormone- over  
follicle-stimulating  
hormone-mediated effects in acute cultures  
of rat granulosa cells

AUTHOR(S): Ohkawa, Reiko; Polan, Mary Lake; Behrman, Harold R.

CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, 06510, USA

SOURCE: Endocrinology (1985), 117(1), 248-54

CODEN: ENDOAO; ISSN: 0013-7227

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Adenosine [58-61-7] rapidly increased ATP [56-65-5] levels in cultured rat granulosa cells. This effect was maximal (.apprx.2-fold) within 60 min of culture and occurred in the absence or presence of **FSH** [9002-68-0] or **LH** [9002-67-9]. The increase in granulosa cell ATP levels by adenosine was dose-dependent, with half-maximal and maximum responses of 10 and 30 µM adenosine, resp. **Dipyridamole** (10 µM), a purine transport inhibitor, blocked the adenosine-dependent increase in granulosa cell ATP levels. Adenosine and 5'-AMP [61-19-8] were equipotent in increasing cell ATP levels; adenine [73-24-5] also increased ATP levels, but was significantly less active (.apprx.50% of adenosine), whereas hypoxanthine, inosine, and xanthine were inactive. **FSH** consistently decreased granulosa cell ATP levels by .apprx.30% in the absence or presence of adenosine, whereas **LH** had no effect on cell levels of ATP. Both **FSH** and **LH** stimulated cAMP [60-92-4] accumulation in granulosa cells, but the maximal response to **FSH** was substantially greater than that to **LH**. Adenosine amplified cAMP accumulation in response to both **FSH** and **LH**, but the effect of adenosine on this response to **FSH** was modest. Amplification

by adenosine of cAMP accumulation in response to LH was substantial and .apprx.2-3-fold greater than that seen with FSH. Since adenosine augments LH-dependent cAMP accumulation to a greater extent than FSH-stimulated cAMP production, adenosine may favor premature follicular luteinization and, perhaps, function as a mediator of atresia in the developing follicle.

IT 9002-67-9 9002-68-0

RL: BIOL (Biological study)

(ovary follicle response to, adenosine effect on)

L56 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 18 Aug 1984

ACCESSION NUMBER: 1984:448976 HCAPLUS

DOCUMENT NUMBER: 101:48976

TITLE: Interactions of a phosphodiesterase inhibitor, 3-isobutyl-1-methyl xanthine, with prostaglandin E2, follicle-stimulating hormone, luteinizing hormone, and dibutyryl cyclic 3',5'-adenosine monophosphate (cAMP) in cAMP and steroid production by neonatal rat ovaries in vitro

AUTHOR(S): Reddoch, Robert B.; Armstrong, David T.

CORPORATE SOURCE: Dep. Physiol. Obs., Univ. West. Ontario, London, ON, N6A 5A5, Can.

SOURCE: Endocrinology (1984), 115(1), 11-18

CODEN: ENDOAO; ISSN: 0013-7227

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The development of responsiveness to PGE2 [363-24-6], FSH [9002-68-0], LH [9002-67-9], and dibutyryl cAMP ((Bu)2cAMP) [362-74-3] was examined in whole ovaries isolated from neonatal Sprague-Dawley rats on days 0 (birth), 2, 4, or 6 postpartum. Pairs of ovaries were incubated with these stimuli in the absence or presence of 3-isobutyl-1-methylxanthine (MIX), a potent phosphodiesterase [9025-82-5] inhibitor, and accumulations in the medium of cAMP [60-92-4], androstenedione [63-05-8], and estradiol [50-28-2] were measured. PGE2 stimulated marked cAMP accumulation on day 0 whereas similar responses to FSH and LH did not develop until days 2 and 4, resp. No cAMP accumulation was detectable in the absence of MIX. Ovaries gradually acquired the ability to produce both cAMP and steroids in response to FSH and LH over the 1st postnatal week. No steroid accumulation was measurable in incubations conducted on days 0 or 2; however, steroidogenesis was stimuable in day-4 ovaries by (Bu)2cAMP. PGE2, FSH, and LH also stimulated steroid accumulation on day 4, but only when MIX was present in the incubation, suggesting that high levels of endogenous cAMP can also lead to steroid production. By day 6, all stimuli elicited steroid accumulation in a dose-dependent fashion. MIX potentiated the responses to lower doses of these stimuli but not to the higher doses at this age. In the absence of MIX, LH was .apprx.100-fold more potent than FSH in stimulating steroid production; however, the 2 gonadotropins were nearly equipotent in this regard when MIX was present in the incubation. Apparently, a cAMP-sensitive steroidogenic apparatus is present in the rat ovary as early as the 4th day postpartum. Because of the marked effects of MIX on gonadotropin-induced steroidogenesis, it may be that modulation of phosphodiesterase

activity is 1 way by which steroidogenesis is regulated in the neonatal rat ovary.

IT 9002-67-9 9002-68-0

RL: BIOL (Biological study)

(cAMP and steroid formation response to, in ovary of newborn)

IT 9025-82-5

RL: BIOL (Biological study)

(of ovary, of newborn, gonadotropin-induced steroidogenesis in relation to)

L56 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 07 Jul 1984

ACCESSION NUMBER: 1984:401193 HCAPLUS

DOCUMENT NUMBER: 101:1193

TITLE: Cyclic GMP phosphodiesterase and guanylate cyclase activities in rabbit ovaries and the effect of in-vivo stimulation with LH

AUTHOR(S): Patwardhan, V. V.; Lanthier, A.

CORPORATE SOURCE: Lab. Endocrinol., Hop. Notre-Dame, Montreal, QC, H2L 4K8, Can.

SOURCE: Journal of Endocrinology (1984), 101(3), 305-10  
CODEN: JOENAK; ISSN: 0022-0795

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Injection of LH [9002-67-9] (50 µg) i.v. to rabbits decreased the guanylate cyclase [9054-75-5] activity of ovarian cytosol and particulate fractions but had no effect on ovarian cGMP phosphodiesterase [9068-52-4] activity. Evidently, this fall in cyclase activity is responsible for previously observed LH-induced decreases in ovary cGMP [7665-99-8] concentration

IT 9002-67-9

RL: BIOL (Biological study)

(cGMP phosphodiesterase and guanylate cyclase of ovary response to)

IT 9068-52-4

RL: BIOL (Biological study)

(of ovary, LH effect on)

L56 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 12 May 1984

ACCESSION NUMBER: 1979:483808 HCAPLUS

DOCUMENT NUMBER: 91:83808

TITLE: The influence of follicular fluid on progesterone secretion by porcine granulosa cells in vitro

AUTHOR(S): Ledwitz-Rigby, Florence; Rigby, Brian W.

CORPORATE SOURCE: Dep. Biol. Sci., Northern Illinois Univ., DeKalb, IL, 60115, USA

SOURCE: Advances in Experimental Medicine and Biology (1979), 112 (Ovarian Follicular Corpus Luteum Funct.), 347-59

CODEN: AEMBAP; ISSN: 0065-2598

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Porcine follicular fluid contains at least 2 factors which can modify porcine granulosa cell function in vitro. One factor, found primarily in fluid from 1-2 mm follicles inhibited LH [9002-67-9]-stimulated cyclic AMP [60-92-4] accumulation, basal and LH-stimulated progesterone [57-83-0] secretion, and morphol. luteinization of granulosa cells from medium sized (3-5

mm) and large (6-12 mm) follicles. Following inhibition by the follicular fluid luteinization inhibitor, incubation with both **LH** and a phosphodiesterase [9025-82-5] inhibitor partially restored cyclic AMP accumulation and fully restored progesterone secretion. Another factor found primarily in fluid from large preovulatory follicles stimulated basal and gonadotropin-stimulated progesterone secretion by granulosa cells from small antral follicles. It may be necessary for the fluid within an individual follicle to shift from being inhibitory of luteinization to being permissive or **stimulatory** for the granulosa cells to mature rather than become **atretic**.

IT 9002-67-9

RL: BIOL (Biological study)

(cyclic AMP production and progesterone secretion by granulosa cell response to, ovary follicular fluid effect on)

IT 9025-82-5

RL: BIOL (Biological study)

(in ovary follicular fluid effect on cyclic AMP production and progesterone secretion)

L56 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 12 May 1984

ACCESSION NUMBER: 1979:483693 HCAPLUS

DOCUMENT NUMBER: 91:83693

TITLE: Gonadotropin action in isolated ovarian luteal cells: the intermediate role of adenosine 3', 5'-cyclic monophosphate in hormonal stimulation of progesterone synthesis

AUTHOR(S): Sala, G. B.; Dufau, Maria L.; Catt, Kevin J.  
CORPORATE SOURCE: Endocrinol. Reprod. Res. Branch, NIH, Bethesda, MD, 20014, USA

SOURCE: Advances in Experimental Medicine and Biology (1979), 112 (Ovarian Follicular Corpus Luteum Funct.), 489-95

CODEN: AEMBAP; ISSN: 0065-2598

DOCUMENT TYPE: Journal

LANGUAGE: English

AB CAMP [60-92-4] formation by isolated rat luteal cells was increased by human **chorionic gonadotropin** (hCG) [9002-61-3] in the presence or absence of the phosphodiesterase [9025-82-5] inhibitor, 1-methyl-3-isobutylxanthine. CAMP binding by the protein kinase [9026-43-1] receptor and intracellular and extracellular CAMP also increased with hCG application and dosage. Progesterone [57-83-0] production followed a similar path and was higher in the absence of the phosphodiesterase inhibitor. The adenylate cyclase-protein kinase enzyme sequence may have a role in the mediation of gonadotropin action in luteal cells.

IT 9025-82-5

RL: BIOL (Biological study)

(in progesterone formation stimulation by gonadotropin)

IT 9002-61-3

RL: BIOL (Biological study)

(progesterone formation stimulation by, in corpus luteum, cyclic AMP in)

L56 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 12 May 1984

ACCESSION NUMBER: 1978:594428 HCAPLUS

DOCUMENT NUMBER: 89:194428

10/817312

TITLE: Interactions of gonadotropins with corpus luteum membranes. II. The identification of two distinct surface membrane fractions from superovulated rat ovaries  
AUTHOR(S): Bramley, Thomas A.; Ryan, Robert J.  
CORPORATE SOURCE: Dep. Mol. Med., Mayo Clin. and Mayo Found., Rochester, MN, USA  
SOURCE: Endocrinology (1978), 103(3), 796-804  
CODEN: ENDOAO; ISSN: 0013-7227  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Fractions enriched in human chorionic gonadotropin (I)-binding activity were prepared by differential rate centrifugation of superovulated rat ovarian homogenates and were applied to continuous sucrose d. gradients (20-55%). After centrifugation at 63,000 gav for 3.5 h, fractions of each gradient were collected and assayed for a range of marker enzyme activities characteristic of surface membranes and subcellular organelles. Mitochondria, lysosomes, and rough and smooth endoplasmic reticulum membranes accumulated in the gradient between 38-41% sucrose (1.165-1.180 g/cm<sup>3</sup>). Nuclei passed through the gradient. However, the various surface membrane markers concentrated in 2 distinct regions of the gradient. Alkaline phosphatase, phosphodiesterase, (Na<sup>+</sup> + K<sup>+</sup>)ATPase I, and I-binding activity concentrated at 29-32% sucrose (1.120-1.135 g/cm<sup>3</sup>), whereas 5'-nucleotidase, Mg<sup>2+</sup>-dependent ATPase, and adenylate cyclase activities (and minor peaks of I-binding and phosphodiesterase activities) were enriched at 36-8% sucrose (1.16-1.17 g/cm<sup>3</sup>). A 2nd ATPase [(Na<sup>+</sup> + K<sup>+</sup>)ATPase II] was also observed in this region of the gradient, which could be distinguished from (Na<sup>+</sup> + K<sup>+</sup>)ATPase I of the light membrane fraction by its sensitivity to the Ca<sup>2+</sup>-chelating agent EGTA. The kinetics of binding of radioiodinated I to the gonadotropin receptors of the light and heavy membrane fractions were very similar. Evidently, fractionation of superovulated rat ovaries yields 2 distinct populations of surface membrane material which have distinct densities and marker enzyme profiles. Furthermore, in contrast to the heavy membrane fraction, light membranes seem to possess considerable amts. of I receptor activity but very little adenylate cyclase.

IT 9025-82-5  
RL: BIOL (Biological study)  
(of corpus luteum membrane, chorionic gonadotropin receptors in relation to)

IT 9002-61-3  
RL: BIOL (Biological study)  
(receptors for, of corpus luteum membrane, enzyme in relation to)

L56 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 12 May 1984

ACCESSION NUMBER: 1978:594427 HCAPLUS

DOCUMENT NUMBER: 89:194427

TITLE: Interactions of gonadotropins with corpus luteum membranes. I. Properties and distributions of some marker enzyme activities after subcellular fractionation of the superovulated rat ovary

AUTHOR(S): Bramley, Thomas A.; Ryan, Robert J.  
CORPORATE SOURCE: Dep. Mol. Med., Mayo Med. Sch., Rochester, MN, USA  
SOURCE: Endocrinology (1978), 103(3), 778-95  
CODEN: ENDOAO; ISSN: 0013-7227  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The properties of a number of enzyme activities of the superovulated rat ovary were studied to establish optimal assay conditions and specific assay procedures for each activity. The activities were chosen on the basis of their extensive use in other tissues of the rat as marker enzymes for the major cell organelles. Homogenates of superovulated rat ovaries were subjected to fractionation by differential rat centrifugation, and sedimentation profiles were constructed for each marker enzyme activity. The various subcellular fractions were also monitored by electron microscopy. The enrichment of fractions with particular organelles by electron microscopy and enrichment of the appropriate organelle marker enzyme activities correlated well. Sedimentation profiles of a number of plasma membrane marker enzymes demonstrated a marked discrepancy between human **chorionic gonadotropin** (I)-binding activity and 5'-nucleotidase, alkaline phosphatase, and Mg<sup>2+</sup>-dependent ATPase on the 1 hand and basal, I-stimulated, and F--stimulated adenylate cyclase activities on the other hand. Fractions enriched in I-binding and adenylate cyclase activities were subjected to further fractionation on discontinuous sucrose d. gradients. The distributions of the various plasma membrane markers again indicated a partial dissociation between I-binding and adenylate cyclase activities of luteinized rat ovaries, suggesting the existence of 2 distinct major plasma membrane populations, with different buoyant densities, marker enzyme profiles, and adenylate cyclase and hormone-binding levels.

IT 9025-82-5

RL: PROC (Process)

(of corpus luteum, subcellular distribution of, **chorionic gonadotropin** receptors in relation to)

IT 9002-61-3

RL: BIOL (Biological study)

(receptors for, of corpus luteum, subcellular distribution of, enzyme in relation to)

L56 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 12 May 1984

ACCESSION NUMBER: 1976:99807 HCAPLUS

DOCUMENT NUMBER: 84:99807

TITLE: Stimulatory effect of **FSH** in vitro on the extracellularly active cyclic AMP phosphodiesterase in the prepubertal rat ovary  
 AUTHOR(S): Selstam, Gunnar; Rosberg, Sten  
 CORPORATE SOURCE: Dep. Physiol., Univ. Goteborg, Goteborg, Swed.  
 SOURCE: Acta Endocrinologica (1976), 81(3), 563-73  
 CODEN: ACENA7; ISSN: 0001-5598

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **FSH** [9002-68-0] (0.1-100 µg/ml), but not **LH**, stimulated cyclic AMP phosphodiesterase [9036-21-9] activity in ovarian preps. Kinetic data are given, and differences in the effects **FSH** and **LH** on the cyclic AMP system of the prepubertal rat ovary are discussed.

IT 9002-68-0

RL: BIOL (Biological study)

(cyclic AMP phosphodiesterase of ovary stimulation by, before puberty)

IT 9036-21-9

RL: PROC (Process)

(of ovary, **FSH** stimulation of, before puberty)

10/817312

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,  
JICST-EPLUS, JAPIO' ENTERED AT 12:52:58 ON 07 APR 2005)

L57 230 S L50  
L58 117 S L51  
L59 302 S L52  
L60 65 S (L57 OR L58 OR L59) AND ((OOCYTE OR OVOCYT?) (S) PRODUC? OR  
OR (OVARI## OR ATRETIC OR GRAAFIAN OR  
FOLLICUL?) (S) (HYPERSTIMULAT?  
OR STIMULAT?) OR OVULAT?)  
L61 81 S (L57 OR L58 OR L59) AND FEMALE  
L62 26 S L61 AND (STERIL? OR INFERTIL? OR FERTIL?)  
L63 79 S L60 OR L62  
L64 56 DUP REM L63 (23 DUPLICATES REMOVED)

L64 ANSWER 1 OF 56 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation  
on STN

ACCESSION NUMBER: 2005:150939 SCISEARCH

THE GENUINE ARTICLE: 893CA

TITLE: Fundamental significance of specific  
phosphodiesterases in the control of spontaneous  
meiotic resumption in porcine oocytes

AUTHOR: Laforest M F; Pouliot E; Gueguen L; Richard F J  
(Reprint)

CORPORATE SOURCE: Univ Laval, Fac Sci Agr & Alimentat, Dept Anim Sci,  
Ctr Rech Biol Reprod, St Foy, PQ G1K 7P4, Canada  
(Reprint)

COUNTRY OF AUTHOR: Canada

SOURCE: MOLECULAR REPRODUCTION AND DEVELOPMENT, (MAR 2005)  
Vol. 70, No. 3, pp. 361-372.  
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111  
RIVER ST, HOBOKEN, NJ 07030 USA.  
ISSN: 1040-452X.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 63

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB The meiosis of mammalian oocytes begins during the fetal life and  
stops at the dictyate stage. This study has assessed the role of  
specific phosphodiesterase (PDE) inhibitors on the control of meiotic  
resumption in porcine oocytes investigating the influence of PMSG-  
hCG and cAMP stimulation. Cumulus-oocytes complexes  
(COCs) and denuded oocytes (DOs) were collected from gilt  
ovaries obtained at a local slaughterhouse. Oocytes were  
cultured in NCSU23 with different PDE inhibitors. The EC50 for oocytes  
maintained in germinal vesicle (GV) stage was evaluated using  
different doses of both cilostamide (CIL), PDE3 inhibitor and  
3-isobutyl-1-methylxanthine (IBMX), a nonspecific PDE inhibitor. In  
presence of PMSG-hCG, meiotic resumption is observed after  
24 hr of culture. Both CIL and IBMX reversibly blocked meiotic  
resumption. In absence of PMSG-hCG, meiotic resumption is  
reduced after 24 hr of culture. After 48 hr of culture, only CIL  
significantly blocked meiotic resumption. Still in absence of PMSG-  
hCG, significant effect of treatment was only observed in COCs  
using the combination of CIL and rolipram (PDE3 and PDE4  
inhibitor, respectively) compared to the use of IBMX. To assess the  
contribution of cAMP synthesis, a low dose of an adenylyl cyclase (AC)  
stimulator, forskolin, has been used in combination with CIL  
showing a significant effect of this combination. In CIL-treated COCs  
and DOs, significant higher percentages of oocytes were maintained in



GV stage when cultured in combination with forskolin instead of PMSG-hCG. In conclusion, these results demonstrate that the control of meiotic resumption in porcine oocytes is highly regulated by cAMP. Both the degradation by specific PDE3 enzyme and the synthesis by an active AC are highly involved. (C) 2005 Wiley-Liss, Inc.

L64 ANSWER 2 OF 56 MEDLINE on STN DUPLICATE 1  
 ACCESSION NUMBER: 2004625557 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 15448112  
 TITLE: Pharmacological inhibition of **phosphodiesterase 4** triggers **ovulation** in **follicle-stimulating hormone**-primed rats.  
 AUTHOR: McKenna Sean D; Pietropaolo Michael; Tos Enrico Gillio; Clark Ann; Fischer David; Kagan David; Bao Bagna; Chedrese P Jorge; Palmer Stephen  
 CORPORATE SOURCE: Serono Reproductive Biology Institute, Rockland, Massachusetts 02370, USA.. sean.mckenna@serono.com  
 SOURCE: Endocrinology, (2005 Jan) 146 (1) 208-14. Electronic Publication: 2004-09-24.  
 Journal code: 0375040. ISSN: 0013-7227.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200501  
 ENTRY DATE: Entered STN: 20041220  
 Last Updated on STN: 20050119  
 Entered Medline: 20050118

AB Phosphodiesterases (PDEs) are a family of enzymes that hydrolyze cyclic nucleotides to render them biologically inactive. As such, these enzymes are critical regulators of signal transduction pathways that use cyclic nucleotides as second messengers. **PDE4** is one such member that has been identified in ovarian tissue and purported to have a role in the regulation of gonadotropin action. In the present study, selective **PDE4** inhibitors enhanced intracellular signaling in a human **LH** receptor-expressing granulosa cell line. In vivo, **PDE4** inhibition in **FSH**-primed rats resulted in **ovulation**, indicating that the **PDE4** inhibitors can substitute for **LH** and human **chorionic gonadotropin** (**hCG**) in this process. Moreover, when coadministered with a subeffective dose of **hCG**, **PDE4** inhibitors acted synergistically to enhance the **ovulation** response. Inhibitors of **PDE3** or **PDE5** had no **ovulatory** effect under similar conditions. Oocytes that were **ovulated** after **PDE4** inhibition could be fertilized in vitro at a rate similar to that of oocytes from **hCG**-induced **ovulation**. Moreover, such oocytes were fully capable of being fertilized in vivo and developing into normal live pups. These results indicate that small molecule **PDE4** inhibitors may be orally active alternatives to **hCG** as part of a fertility treatment regimen.

L64 ANSWER 3 OF 56 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2004-757710 [74] WPIDS  
 DOC. NO. CPI: C2004-265816  
 TITLE: Use of a phosphodiesterase enzyme inhibitor for **stimulating ovarian follicular growth** in a female.

10/817312

DERWENT CLASS: B02 B04  
INVENTOR(S): ARKINSTALL, S J; ESHKOL, A; MACNAMEE, M C; MCKENNA, S D; PALMER, S S  
PATENT ASSIGNEE(S): (ARKI-I) ARKINSTALL S J; (ESHK-I) ESHKOL A; (MACN-I) MACNAMEE M C; (MCKE-I) MCKENNA S D; (PALM-I) PALMER S S; (ISTF) ARS APPLIED RES SYSTEMS HOLDING NV  
COUNTRY COUNT: 108  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004087211	A2	20041014	(200474)*	EN	89
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2004259792	A1	20041223	(200504)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004087211	A2	WO 2004-US10346	20040401
US 2004259792	A1	Provisional	US 2003-458955P
		Provisional	US 2003-470434P
		Provisional	US 2004-540301P
		Provisional	US 2004-544003P
			US 2004-817312

PRIORITY APPLN. INFO: US 2004-544003P 20040212; US  
2003-458955P 20030401; US  
2003-470434P 20030515; US  
2004-540301P 20040128; US  
2004-817312 20040401

AN 2004-757710 [74] WPIDS  
AB WO2004087211 A UPAB: 20041117  
NOVELTY - Use of a phosphodiesterase enzyme inhibitor (I) for the preparation of a medicament (M) for **stimulating ovarian follicular** growth in a female is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) increasing follicle maturation comprising treating a **female** with a composition (C1) comprising (I) to **stimulate follicular** maturation;

(2) increasing oocyte maturation comprising treating an oocyte in vitro with a composition (C2) comprising (I) to cause oocyte maturation;

(3) a vial containing a single dose of a mixture of phosphodiesterase type 4 inhibitor (I') and **follicle stimulating hormone (FSH)**; and

(4) a kit (II) for treating **infertility** comprising a first composition comprising at least one of (I') in a formulation and a second composition comprising **FSH** in a formulation.

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ACTIVITY - Antiinfertility.

MECHANISM OF ACTION - Phosphodiesterase inhibitor.

USE - (I) is useful in medicaments for **stimulating ovarian follicular growth** in a **female** undergoing **ovulation** induction (particularly controlled **ovarian hyperstimulation**). (I) is useful for increasing follicle maturation and for increasing oocyte maturation in vitro.

The biological efficacy of (I), in combination with low doses of **FSH**, to **stimulate ovarian follicular growth** was tested in rats. **Sildenafil** (an inhibitor of PDE's 1, 5, and 6) administered subcutaneously in NP3S at doses of 1, 5, and 25 mg/kg x 4 injections per rat in conjunction with **FSH** low dose gave an average number of oocytes per rat of 3.5, 5.5 and 6.9 respectively, and 6 out of 8, 5 out 8, and 7 out of 8 rats **ovulated** respectively. In contrast, when the **FSH** low dose was administered alone with NP3S vehicle, an average of 1 oocyte per rat was collected, and only 3 out of ten rats **ovulated**.

(NP3S = 5% n-methyl-2-pyrrolidone, 30% polyethylene glycol 400, 25% polyethylene glycol 200, 20% propylene glycol and 20% saline).

ADVANTAGE - The in vitro maturation protocol involves a significant reduction/elimination of the side effects and utilizes reduced amounts of hormones for the treatment.

Dwg.0/15

L64 ANSWER 4 OF 56 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2004-330136 [30] WPIDS  
DOC. NO. CPI: C2004-125059  
TITLE: New 2-carboxamide piperazine derivatives are  
**follicle stimulating hormone** receptor agonists, useful for  
treating **infertility**.  
DERWENT CLASS: B02 B03  
INVENTOR(S): GOUTOPOULOS, A; LIAO, Y; MAGAR, S; RUSSELL, T J;  
SCHWARZ, M  
PATENT ASSIGNEE(S): (ISTF) ARS APPLIED RES SYSTEMS HOLDING NV  
COUNTRY COUNT: 106  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004031182	A1	20040415	(200430)*	EN	62
RW:	AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE				
	LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW				
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE				
	DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE				
	KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO				
	NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ				
	UA UG US UZ VC VN YU ZA ZM ZW				
AU 2003299124	A1	20040423	(200465)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004031182	A1	WO 2003-EP50640	20030919
AU 2003299124	A1	AU 2003-299124	20030919

FILING DETAILS:

Searcher : Shears 571-272-2528

PATENT NO	KIND	PATENT NO
AU 2003299124	A1 Based on	WO 2004031182

PRIORITY APPLN. INFO: US 2002-412308P 20020920

AN 2004-330136 [30] WPIDS

AB WO2004031182 A UPAB: 20040511

NOVELTY - 2-Carboxamide piperazine derivatives (I) and their salts are new.

DETAILED DESCRIPTION - 2-Carboxamide piperazine derivatives of formula (I) and their salts are new.

R1, R2 = H, 1-12C alkyl, 2-12C alkenyl, 2-12C alkynyl (all optionally interrupted by a heteroatom of O, N or S), (hetero)aryl, 3-8 membered cycloalkyl, heterocycloalkyl (all optionally fused with 1-2 further (hetero)cycloalkyl, (hetero)aryl), an acyl moiety, 1-12C alkyl (hetero)aryl, 1-12C alkenyl (hetero)aryl, 1-12C alkynyl (hetero)aryl, 1-12C alkyl (hetero)cycloalkyl, alkoxycarbonyl, aminocarbonyl, 1-12C carboxy, 1-12C alkyl acyl, (hetero)aryl acyl, 3-8C (hetero)cycloalkyl acyl, 1-12C alkyl acyloxy, 1-12C alkyl alkoxy, 1-12C alkyl alkoxycarbonyl, 1-12C alkyl aminocarbonyl, 1-12C alkyl acylamino, acylamino, 1-12C alkyl ureido, 1-12C alkyl carbamate, 1-12C alkyl amino, 1-12C alkyl ammonium, 1-12C alkyl sulfonyloxy, 1-12C alkyl sulfonyl, 1-12C alkyl sulfinyl, 1-12C alkyl sulfanyl, 1-12C alkyl sulfonylamino or 1-12C alkyl aminosulfonyl;

R3 = 1-16C alkyl, 2-16C alkenyl, 2-16C alkynyl (all optionally interrupted by a heteroatom of O, N or S), (hetero)aryl, 3-8C cycloalkyl, heterocycloalkyl (all optionally fused with 1-2 further (hetero)cycloalkyl, (hetero)aryl), an acyl moiety, 1-16C alkyl (hetero)aryl, 2-16C alkenyl (hetero)aryl, 2-16C alkynyl (hetero)aryl, 1-16C alkyl (hetero)cycloalkyl, 2-16C alkenyl heterocycloalkyl, 2-16C alkynyl (hetero)cycloalkyl, alkoxycarbonyl, aminocarbonyl, 1-16C alkyl carboxy, 1-16C alkyl acyl, (hetero)aryl acyl, 3-8 membered (hetero)cycloalkyl acyl, 1-16C alkyl acyloxy, 1-16C alkyl alkoxy, 1-16C alkyl alkoxycarbonyl, 1-16C alkyl aminocarbonyl, 1-16C alkyl acylamino, acylamino, 1-16C alkyl ureido, 1-16C alkyl carbamate, 1-16C alkyl amino, 1-16C alkyl ammonium, 1-16C alkyl sulfonyloxy, 1-16C alkyl sulfonyl, 1-16C alkyl sulfinyl, 1-16C alkyl sulfanyl, 1-16C alkyl sulfonylamino or 1-16C alkyl aminosulfonyl; and

R4 = 1-12C alkyl, 2-12C alkenyl, 2-12C alkynyl (all optionally interrupted by a heteroatom of O, N or S, (hetero)aryl (optionally fused with 1-2 further (hetero)cycloalkyl, (hetero)aryl or amino)) or 3-8 membered (hetero)cycloalkyl (optionally fused with 1-2 further (hetero)cycloalkyl, (hetero)aryl or amino).

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I) packaged together with instructions for the use of (I).

ACTIVITY - Antiinfertility; Contraceptive; Gynecological.

MECHANISM OF ACTION - **Follicle stimulating****hormone (FSH) receptor agonist;****Phosphodiesterase 4 (PDE4) receptor****inhibitor; Adenosine transporter inhibitor; Prostanoid receptor inhibitor.**

(I) were tested for their **follicle stimulating hormone** receptor agonistic activity in Chinese Hamster Ovary cells (CHO cells). The results showed that the median effective dose (ED50) of 4-octyl-1-(thiophene-2-sulfonyl)-piperazine-2-carboxylic acid(1-ethyl-2-pyridine-3-yl-1H-benzimidazol-5-yl)amide was 13 nM.

USE - (I) are used to treat **infertility** and treat a

subject suffering from or susceptible to a disease or disorder (particularly **ovulatory** disorder in a **female** being treated with an assisted reproduction procedure or undergoing in-vitro **fertilization** and spermatogenesis disorder in male) associated with phosphodiesterase (**PDE4**), adenosine transporters or prostanoid receptors. (All claimed.)  
Dwg.0/0

L64 ANSWER 5 OF 56 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004432434 EMBASE  
TITLE: Drug intervention in early pregnancy after assisted reproductive technology.  
AUTHOR: Ozturk O.; Saridogan E.; Jauniaux E.  
CORPORATE SOURCE: E. Jauniaux, Acad. Dept. of Obstet./Gynaecology, University College London Hospitals, 86-96 Chenies Mews, London WC1E 6HX, United Kingdom.  
e.jauniaux@ucl.ac.uk  
SOURCE: Reproductive BioMedicine Online, (2004) Vol. 9, No. 4, pp. 452-465.  
Refs: 201  
ISSN: 1472-6483 CODEN: RBOEA6  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 003 Endocrinology  
010 Obstetrics and Gynecology  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
052 Toxicology  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20041021  
Last Updated on STN: 20041021

AB Implantation in humans is a complex, closely regulated, highly selective and relatively poorly understood process. Humans have the highest rate of miscarriage in mammals and various pharmacological manipulations have been used to minimize pregnancy losses in both spontaneous pregnancies and pregnancies resulting from assisted reproduction technology. The widespread application of protocols using numerous drugs in assisted reproduction treatment has led to an increasing number of pregnancies exposed to these drugs. The vast majority of these protocols have been based on data from a few observational and often retrospective clinical studies. This paper reviews the recent literature on drug interventions in early pregnancy after assisted reproduction treatment. It is concluded that there are still numerous issues about the safety of most drugs for both the women and their fetus. In many cases, the benefits are theoretical and the possible long-term side-effects are untested. There is an urgent need for more epidemiological studies and randomized controlled trials to explore the use, efficacy and side-effects of both old and new drugs in early pregnancy after assisted reproduction treatment.

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ACCESSION NUMBER: 2004239702 EMBASE  
TITLE: Gonadotrophin-induced gene regulation in human granulosa cells obtained from IVF patients. Modulation of steroidogenic genes, cytoskeletal genes and genes

coding for apoptotic signalling and protein kinases.

AUTHOR: Sasson R.; Rimón E.; Dantes A.; Cohen T.; Shinder V.; Land-Bracha A.; Amsterdam A.

CORPORATE SOURCE: A. Amsterdam, Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel. [abraham.amsterdam@weizmann.ac.il](mailto:abraham.amsterdam@weizmann.ac.il)

SOURCE: Molecular Human Reproduction, (2004) Vol. 10, No. 5, pp. 299-311.  
Refs: 86  
ISSN: 1360-9947 CODEN: MHREFD

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 010 Obstetrics and Gynecology  
022 Human Genetics  
029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20040628  
Last Updated on STN: 20040628

AB Gonadotrophins exert a major effect on ovarian development and on the control of fertilization. By stimulating cells with forskolin (FK), it is possible to study which genes are activated by gonadotrophins via the cAMP cascade, and which by alternative pathways. Using RNA isolated from stimulated cells, we found that 59% of the total genes modulated by LH were also modulated by FK, while 69% of the genes modulated exclusively by FSH were also modulated by FK. Gene transcripts involved in steroidogenesis/progesterone production were highly elevated, while 17 $\beta$ -hydroxysteroid dehydrogenase was down-regulated. This suggests that a decrease in the conversion of androstenedione to testosterone and estrone to estradiol occurs during luteinization. Down-regulation of genes coding for actin cytoskeleton proteins and cytokeratin 18 was observed in response to gonadotrophin and cAMP stimulation. Several of the genes coding for the microtubule network were also modulated, implying that rearrangement of the cytoskeletal proteins permits better coupling between organelles involved in steroidogenesis. A dramatic change in gene transcripts coding for signalling enzymes was observed following LH stimulation. This includes the down-regulation of adenylyl cyclase 7 and 9, elevation of cAMP-dependent phosphodiesterase, and the up-regulation of a negative regulator of G-protein signalling (RGS16) that may negate gonadotrophin signalling via guanine nucleotide binding proteins. Thus luteinized cells, despite increased gene transcripts to LH/chorionic gonadotrophin (CG) receptors, respond inefficiently to gonadotrophin stimulation, due to attenuation of signal transduction in the cAMP cascade at multiple steps. Novel genes involved in the regulation of apoptosis were found for the first time to be up-regulated by gonadotrophin stimulation, including: BAX inhibitor-1, granulysin and apoptosis repressor with caspase recruitment domain (ARC). These proteins may be involved in a unique alternative pathway of ovarian cell death. Such a pathway could temporarily preserve the mitochondria and progesterone production during the initial stages of granulosa cell apoptosis. .COPYRGT, European Society of Human Reproduction and Embryology 2004; all rights reserved.

RESERVED. on STN

ACCESSION NUMBER: 2004331213 EMBASE  
 TITLE: Alternative therapies for male and female sexual dysfunction.  
 AUTHOR: Aung H.H.; Dey L.; Rand V.; Yuan C.-S.  
 CORPORATE SOURCE: Dr. C.-S. Yuan, Tang Center for Herbal Med. Research, Pritzker School of Medicine, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, United States. cyuan@airway.uchicago.edu  
 SOURCE: American Journal of Chinese Medicine, (2004) Vol. 32, No. 2, pp. 161-173.  
 Refs: 72  
 ISSN: 0192-415X CODEN: AJCMBA  
 COUNTRY: Singapore  
 DOCUMENT TYPE: Journal; General Review  
 FILE SEGMENT: 010 Obstetrics and Gynecology  
 028 Urology and Nephrology  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 20040819  
 Last Updated on STN: 20040819  
 AB Sexual dysfunction is prevalent in both men and women. Although new pharmaceutical agents have been identified for male erectile problems, sexual desire and orgasm disorders, individuals with sexual dysfunction often seek alternative therapies, including traditional Chinese medicine. This article reviews currently used alternative therapies, such as herbal medications, L-arginine, acupuncture, biofeedback and others. Potential herb-drug interactions are also presented. .COPYRGT. 2004 World Scientific Publishing Company.

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ACCESSION NUMBER: 2003:334165 BIOSIS  
 DOCUMENT NUMBER: PREV200300334165  
 TITLE: Phosphodiesterase regulation is critical for the differentiation and pattern of gene expression in granulosa cells of the ovarian follicle.  
 AUTHOR(S): Park, Jy-Young; Richard, Francois; Chun, Sang-Young; Park, Jeong-Hoh; Law, Evelyn; Horner, Kathleen; Jin, S.-L. Catherine; Conti, Marco [Reprint Author]  
 CORPORATE SOURCE: Division of Reproductive Biology, Department of Obstetrics and Gynecology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA, 94305-5317, USA  
 marco.conti@stanford.edu  
 SOURCE: Molecular Endocrinology, (June 2003) Vol. 17, No. 6, pp. 1117-1130. print.  
 ISSN: 0888-8809 (ISSN print).  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 23 Jul 2003  
 Last Updated on STN: 23 Jul 2003  
 AB Feedback regulations are integral components of the cAMP signaling required for most cellular processes, including gene expression and cell differentiation. Here, we provide evidence that one of these feedback regulations involving the cyclic nucleotide phosphodiesterase

PDE4D plays a critical role in cAMP signaling during the differentiation of granulosa cells of the ovarian follicle. Gonadotropins induce PDE4D mRNA and increase the cAMP hydrolyzing activity in granulosa cells, demonstrating that a feedback regulation of cAMP is operating in granulosa cells in vivo. Inactivation of the PDE4D by homologous recombination is associated with an altered pattern of cAMP accumulation induced by the gonadotropin LH/human chorionic gonadotropin (hCG), impaired female fertility, and a markedly decreased ovulation rate. In spite of a disruption of the cAMP response, LH/hCG induced P450 side chain cleavage expression and steroidogenesis in a manner similar to wild-type controls. Morphological examination of the ovary of PDE4D<sup>-/-</sup> mice indicated luteinization of antral follicles with entrapped oocytes. Consistent with the morphological finding of unruptured follicles, LH/hCG induction of genes involved in ovulation, including cyclooxygenase-2, progesterone receptor, and the downstream genes, is markedly decreased in the PDE4D<sup>-/-</sup> ovaries. These data demonstrate that PDE4D regulation plays a critical role in gonadotropin mechanism of action and suggest that the intensity and duration of the cAMP signal defines the pattern of gene expression during the differentiation of granulosa cells.

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STN DUPLICATE 2

ACCESSION NUMBER: 2003:560776 BIOSIS  
DOCUMENT NUMBER: PREV200300561423  
TITLE: Study on the relationship between endometrial thickness and uterine radial artery impedance: Vaginal sildenafil improves both values.  
AUTHOR(S): Shimamura, Katsunori [Reprint Author]; Takasaki, Akihisa [Reprint Author]; Tamura, Hiroshi [Reprint Author]; Mirioka, Hitoshi [Reprint Author]  
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Saiseikai Shimonoseki General Hospital, Shimonoseki, Japan  
SOURCE: Japanese Journal of Fertility and Sterility, (October 2003) Vol. 48, No. 3-4, pp. 99-105. print.  
CODEN: NFGZAD. ISSN: 0029-0629.  
DOCUMENT TYPE: Article  
LANGUAGE: Japanese  
ENTRY DATE: Entered STN: 26 Nov 2003  
Last Updated on STN: 26 Nov 2003

AB The aim of this study was to investigate the relationship between endometrial thickness and uterine radial artery impedance on the day of human chorionic gonadotropin (hCG) administration, and to evaluate the effect of vaginal sildenafil (viagra) administration in patients with a thin endometrium and high impedance. Eighty-three infertile patients who gave their informed consent were enrolled in this study, and divided to two groups: endometrium of  $\geq 8$  mm (group A, n=70) and endometrium of  $< 8$  mm (group B, n=13). There was a significant negative correlation between the uterine radial artery resistance index (RI) and endometrial thickness. The RI was significantly higher in the group B than in the group A. Five patients with thin endometrium and high RI received viagra vaginal tablets (25 mg tabletX4/day). The RI of the uterine radial artery was significantly lower and endometrium was significantly thicker in the viagra treatment cycle than in the previous control cycle. Four of the five patients conceived during the viagra treatment cycle. These results suggest that the impedance



of uterine radial artery is correlated well with the endometrial thickness, and viagra may be an effective drug for improving endometrial thickness in patients with high uterine radial artery impedance.

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 ACCESSION NUMBER: 2003376883 EMBASE  
 TITLE: Study on the relationship between endometrial thickness and uterine radial artery impedance: Vaginal **sildenafil** improves both values.  
 AUTHOR: Shimamura K.; Takasaki A.; Tamura H.; Mirioka H.  
 SOURCE: Japanese Journal of Fertility and Sterility, (2003) Vol. 48, No. 3-4, pp. 19-25.  
 Refs: 14  
 ISSN: 0029-0629 CODEN: NFGZAD  
 COUNTRY: Japan  
 DOCUMENT TYPE: Journal; Article  
 FILE SEGMENT: 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 LANGUAGE: Japanese  
 SUMMARY LANGUAGE: English; Japanese  
 ENTRY DATE: Entered STN: 20031002  
 Last Updated on STN: 20031002

AB The aim of this study was to investigate the relationship between endometrial thickness and uterine radial artery impedance on the day of human **chorionic gonadotropin** (hCG) administration, and to evaluate the effect of vaginal **sildenafil** (viagra) administration in patients with a thin endometrium and high impedance. Eighty-three **infertile** patients who gave their informed consent were enrolled in this study, and divided to two groups: endometrium of  $\geq 8$  mm (group A, n = 70) and endometrium of  $< 8$  mm (group B, n = 13). There was a significant negative correlation between the uterine radial artery resistance index (RI) and endometrial thickness. The RI was significantly higher in the group B than in the group A. Five patients with thin endometrium and high RI received viagra vaginal tablets (25 mg tablet x 4/day). The RI of the uterine radial artery was significantly lower and endometrium was significantly thicker in the viagra treatment cycle than in the previous control cycle. Four of the five patients conceived during the viagra treatment cycle. These results suggest that the impedance of uterine radial artery is correlated well with the endometrial thickness, and viagra may be an effective drug for improving endometrial thickness in patients with high uterine radial artery impedance.

L64 ANSWER 11 OF 56 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN  
 ACCESSION NUMBER: 2003110451 EMBASE  
 TITLE: The present and future state of hormonal treatment for male **infertility**.  
 AUTHOR: Liu P.Y.; Handelsman D.J.  
 CORPORATE SOURCE: D.J. Handelsman, Department of Andrology, Concord Hospital/ANZAC Res. Inst., University of Sydney, Concord, NSW 2139, Australia. djh@med.usyd.edu.au  
 SOURCE: Human Reproduction Update, (2003) Vol. 9, No. 1, pp. 9-23.  
 Refs: 194  
 ISSN: 1355-4786 CODEN: HRUPF8

10/817312

COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 003 Endocrinology  
021 Developmental Biology and Teratology  
028 Urology and Nephrology  
030 Pharmacology  
036 Health Policy, Economics and Management  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20030327  
Last Updated on STN: 20030327

AB Although male factors contribute to over half of all cases of **infertility**, most **infertile** men are described as 'idiopathic oligo/asthenozoospermic' rather than diagnosed precisely; hence, specific medical treatment is not possible. One uncommon but treatable cause of male **infertility** is gonadotrophin deficiency in which gonadotrophin replacement therapy is highly effective at inducing spermatogenesis and **fertility**. Hormonal therapy is a logical approach for empirical drug therapy given the fundamental role of hormonal regulation in spermatogenesis. However, treatment with GnRH analogues, gonadotrophins, androgens, anti-estrogens, aromatase inhibitors, growth hormone- and prolactin-suppressing drugs is ineffective in unselected **infertile** men. Prolonged high-dose glucocorticoid therapy for sperm autoimmunity may improve pregnancy rates modestly, but the risks are generally unacceptable compared with IVF or ICSI. For these reasons, modern reproductive technologies, notably ICSI/IVF, have become the de-facto standard empirical treatment of male **infertility**, despite involving significant though infrequent risks to the fetus and mother. There remains a potential for hormonal methods to improve sperm quality or ultrastructure in subgroups of **infertile** men more responsive to hormonal manipulation or using novel protein or gene-targeted therapies or biochemical approaches based on post-hormonal receptor mechanisms that stimulate spermatogenesis. How such novel hormonal methods will develop in conjunction with improved ICSI/IVF or cloning technologies, and the potential role of adjunctive hormonal therapy remains to be clarified.

L64 ANSWER 12 OF 56 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2002-608152 [65] WPIDS  
CROSS REFERENCE: 2002-556738 [59]  
DOC. NO. CPI: C2002-171756  
TITLE: **Ovulation** induction comprises administering a non-polypeptide cyclic adenosine monophosphate level modulator.  
DERWENT CLASS: B05  
INVENTOR(S): ESHKOL, A; MACNAMEE, M C; MCKENNA, S; PALMER, S; TEPPER, M; MICKENNA, S  
PATENT ASSIGNEE(S): (ESHK-I) ESHKOL A; (MACN-I) MACNAMEE M C; (MCKE-I) MCKENNA S; (PALM-I) PALMER S; (TEPP-I) TEPPER M; (ISTF) ARS APPLIED RES SYSTEMS HOLDING NV  
COUNTRY COUNT: 99  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002103106	A1	20020801	(200265)*		26
WO 2003051344	A1	20030626	(200352)#	EN	

Searcher : Shears 571-272-2528

10/817312

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW  
MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW  
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE  
DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG  
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH  
PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU  
ZA ZW  
AU 2002217111 A1 20030630 (200420)#  
EP 1463493 A1 20041006 (200465)# EN  
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL  
PT RO SE SI TR  
BR 2001017198 A 20041026 (200482)#

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002103106	A1 Provisional CIP of	US 2000-224962P US 2001-928268 US 2001-14812	20000811 20010810 20011214
WO 2003051344	A1	WO 2001-EP14730	20011214
AU 2002217111	A1	WO 2001-EP14730 AU 2002-217111	20011214 20011214
EP 1463493	A1	EP 2001-274987 WO 2001-EP14730	20011214 20011214
BR 2001017198	A	BR 2001-17198 WO 2001-EP14730	20011214 20011214

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002217111	A1 Based on	WO 2003051344
EP 1463493	A1 Based on	WO 2003051344
BR 2001017198	A Based on	WO 2003051344

PRIORITY APPLN. INFO: US 2000-224962P 20000811; US  
2001-928268 20010810; US  
2001-14812 20011214; WO  
2001-EP14730 20011214; AU  
2002-217111 20011214; EP  
2001-274987 20011214; BR  
2001-17198 20011214

AN 2002-608152 [65] WPIDS  
CR 2002-556738 [59]  
AB US2002103106 A UPAB: 20041223

NOVELTY - **Ovulation** induction in a **female** host  
comprises administering a non-polypeptide cyclic adenosine  
monophosphate (cAMP) level modulator (I), optionally prior to the  
luteal phase of the host's **ovulatory** cycle.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a combined treatment for **stimulating**  
**follicular** development and **ovulation** induction in a  
**female** host, comprising administration of an agent which  
increases **follicle stimulating hormone**  
concentrations in the host during the **follicular** phase of  
the host's **ovulatory** cycle and administering a  
non-polypeptide cAMP level modulator (I) to the host prior to the  
luteal phase of the host's **ovulatory** cycle;

Searcher : Shears 571-272-2528

10/817312

(2) **ovulation** induction (M1) in a **female** host comprising the administration of (I) to the host at the time point of an existing **ovulation** induction regimen at which **hCG** or **luteinizing hormone** is administered to the host (Note: CG is defined as **chorionic gonadotropin**);

(3) use of (I) as **ovulation** induction agent;

(4) use of (I) for treating anovulation disorder; and

(5) collecting oocytes for in vitro **fertilization** comprising the administration of (I).

ACTIVITY - Antiinfertility.

In a test carried out on immature **female** rats, mature **ovarian** follicles were generated with a dose of **follicle stimulating hormone. hCG**

(3I U) was administered with and without a single injection of **cis-4-cyano-4-(3-cyclopentyloxy)-4-methoxyphenyl)cyclohexane-1-carboxylic acid (Ia)** (50, 10 and 1 mg/kg). **Ovulation** was determined 18 hours after **hCG** administration by counting the number of ova in the oviduct. A single injection of (Ia) co-administered with **hCG** resulted in an induction of **ovulation**, showing 4 of 6 **ovulated** at 10 mg/kg and 6 out of 6 at 50 mg/kg.

MECHANISM OF ACTION - cAMP Level modulator; Phosphodiesterase inhibitor; Estrogen receptor modulator; Aromatase inhibitor; Inhibitor of related steroidogenic enzymes that results in a decrease in total estrogen production.

USE - For inducing **ovulation** in a **female** host and for collecting oocytes for in vitro **fertilization**, (claimed).  
Dwg.0/10

L64 ANSWER 13 OF 56 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN  
ACCESSION NUMBER: 2002-556738 [59] WPIDS  
CROSS REFERENCE: 2002-608152 [65]  
DOC. NO. CPI: C2002-157815  
TITLE: **Ovulation** induction in host involves administering non-polypeptide cAMP level modulator alone or in combination with human **chorionic gonadotropin/lutenizing hormone** prior to luteal phase of host's **ovulatory** cycle.  
DERWENT CLASS: B05  
INVENTOR(S): ESHKOL, A; MACNAMEE, M C; MCKENNA, S; PALMER, S; TEPPER, M  
PATENT ASSIGNEE(S): (ISTF) ARS APPLIED RES SYSTEMS HOLDING NV; (ESHK-I) ESHKOL A; (MACN-I) MACNAMEE M C; (MCKE-I) MCKENNA S; (PALM-I) PALMER S; (TEPP-I) TEPPER M  
COUNTRY COUNT: 2  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002065324	A1	20020530	(200259)*		20
KR 2004075004	A	20040826	(200505)#		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002065324	A1 Provisional	US 2000-224962P	20000811
		US 2001-928268	20010810

Searcher : Shears 571-272-2528

10/817312

KR 2004075004 A

WO 2001-EP14730

20011214

KR 2004-709259

20040614

PRIORITY APPLN. INFO: US 2000-224962P 20000811; US

2001-928268

20010810; KR

2004-709259

20040614

AN 2002-556738 [59] WPIDS

CR 2002-608152 [65]

AB US2002065324 A UPAB: 20050124

NOVELTY - **Ovulation** (M1) induction in a **female** host, involves administering a non-polypeptide cAMP level modulator to the host especially prior to the luteal phase of the host's **ovulatory** cycle, or at the time point of an existing **ovulation** induction regimen at which human **chorionic gonadotropin** (hCG) or lutenizing hormone (**LH**) is administered to the host.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a combined treatment (M2) for **stimulating follicular** development and **ovulation** induction in a **female** host, involves administering an agent which increases **follicle stimulating hormone** (**FSH**) concentrations in the host during the **follicular** phase of the host's **ovulatory** cycle, and administering the non-polypeptide cAMP level modulator to the host, prior to the luteal phase of the host's **ovulatory** cycle;

(2) a non-polypeptide cAMP level modulator for its use as an **ovulation** induction agent, and in treating an anovulation disorder; and

(3) a pharmaceutical composition containing the above modulator.

ACTIVITY - Antiinfertility.

MECHANISM OF ACTION - Inducer of **ovulation** (claimed).

The effect of cAMP level modulator, PDE inhibitor on **ovulation** in vivo following oral and subcutaneous administration was evaluated. Following **FSH** induced follicular maturation (2.16 IU/rat/injection, bid x 2 days) PDE inhibitor was either injected subcutaneously (subcutis) or administered by oral gavage. **Ovulation** was determined 18 hours after inhibitor administration by counting oocytes in oviduct. Data represented average number of oocytes in oviducts of all rats in each group and frequency of **ovulating** rats. The data demonstrated that administration of PDE inhibitor by either subcutaneous or oral route resulted in an induction of **ovulation** in **FSH** pretreated rats.

USE - The non-polypeptide cAMP level modulator is useful in the manufacture of a medicament for treating anovulatory disorders, and for collecting oocytes for in vitro **fertilization** (claimed). The modulator is useful as a therapeutic agent in replacement of or to enhance the effect of **hCG** or **LH**. (M1) is useful for treating **infertility** in humans and other species.

ADVANTAGE - (M1) is effective in inducing **ovulation** and provides an opportunity of earlier diagnostic testing for pregnancy than current **ovulation** induction regimens involving the use of CG. (M1) provides for the use of lower concentrations of **LH** or CG and thus, lowers **ovarian hyperstimulation** and consequently averts adverse effects associated with the condition such as multiple births, low weight newborns and health complications for the mother.

Dwg.0/10

L64 ANSWER 14 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation  
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ACCESSION NUMBER: 2003:94376 BIOSIS

DOCUMENT NUMBER: PREV200300094376

TITLE: Phosphodiesterase expression targeted to  
gonadotropin-releasing hormone neurons inhibits  
**luteinizing hormone** pulses in  
transgenic rats.

AUTHOR(S): Paruthiyil, Sreenivasan; El Majdoubi, Mohammed; Conti,  
Marco; Weiner, Richard I. [Reprint Author]

CORPORATE SOURCE: Department of Obstetrics, Gynecology, and Reproductive  
Sciences, University of California, San Francisco, CA,  
94143, USA

weinerr@obgyn.ucsf.edu

SOURCE: Proceedings of the National Academy of Sciences of the  
United States of America, (December 24 2002) Vol. 99,  
No. 26, pp. 17191-17196. print.  
ISSN: 0027-8424 (ISSN print).

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Feb 2003

Last Updated on STN: 12 Feb 2003

AB Experiments in the GT1 gonadotropin-releasing hormone (GnRH) cell line  
have shown that the cAMP signaling pathway plays a central role in  
regulating the excitability of the cells. Lowering cAMP levels by  
expressing the constitutively active cAMP-specific phosphodiesterase  
PDE4D1 in GT1 cells inhibited spontaneous Ca<sup>2+</sup> oscillations and  
intrinsic pulsatile GnRH secretion. To address the role of cAMP  
levels in endogenous GnRH neurons, we genetically targeted expression  
of PDE4D1 (P) to GnRH neurons in transgenic rats (R) by using the GnRH  
gene promoter/enhancer regions (G). Three lines of transgenic rats,  
GPR-2, -4, and -5, were established. In situ hybridization and RT-PCR  
studies demonstrated that transgene expression was specifically  
targeted to GnRH neurons. Decreased **fertility** was observed  
in **female** but not in male rats from all three lines. The  
mean **luteinizing hormone** (LH) levels in  
ovariectomized rats were significantly reduced in the GPR-4 and -5  
lines but not in the GPR-2 line. In castrated male and **female**  
GPR-4 rats, the LH pulse frequency was dramatically reduced.  
Six of twelve GPR-4 **females** studied did not **ovulate**  
and had polycystic ovaries. The remaining six **females**  
**ovulated**, but the magnitude of the preovulatory LH  
surge was inhibited by 63%. These findings support the hypothesis  
that cAMP signaling may play a central role in regulating excitability  
of GnRH neurons in vivo. The GPR-4 line of transgenic rats provides a  
genetic model for the understanding of the role of pulsatile  
gonadotropin release in follicular development.

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ACCESSION NUMBER: 2002297017 EMBASE

TITLE: Phosphodiesterase 3 inhibitors selectively block the  
spontaneous resumption of meiosis by macaque oocytes in  
vitro.

AUTHOR: Jensen J.T.; Schwinof K.M.; Zelinski-Wooten M.B.; Conti  
M.; DePaolo L.V.; Stouffer R.L. . . .

CORPORATE SOURCE: J.T. Jensen, Dept. of Obstetrics and Gynecology, Oregon  
Reg. Primate Research Center, Oregon Health and Science

10/817312

University, Portland, OR 97201, United States.  
jensenje@ohsu.edu  
SOURCE: Human Reproduction, (2002) Vol. 17, No. 8, pp.  
2079-2084.  
Refs: 36  
ISSN: 0268-1161 CODEN: HUREEE  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 010 Obstetrics and Gynecology  
029 Clinical Biochemistry  
030 Pharmacology  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20020905  
Last Updated on STN: 20020905  
AB Background: The purpose of this study was to determine whether  
phosphodiesterase (PDE) 3 inhibitors selectively prevent the  
resumption of meiosis in primates. Methods: Immature oocytes (intact  
germinal vesicles) obtained from large pre-ovulatory  
follicles following ovarian stimulation in rhesus  
macaques were incubated with or without various doses of the PDE3  
inhibitors, cilostamide, milrinone or ORG 9935, or a selective  
PDE4 inhibitor, rolipram. Oocytes were observed for germinal  
vesicle breakdown (GVBD) as an indicator of resumption of meiosis.  
Results: At 24 h, 72 of 121 (60%) control oocytes progressed to GVBD  
compared with 9/34 (27%,  $P < 0.01$ ), 4/36 (11.1%,  $P < 0.01$ ) and 0/28  
(0%,  $P < 0.01$ ) oocytes incubated with ORG 9935 at 0.1, 0.5 and 1.0  
 $\mu\text{mol/l}$  respectively. Similar results were achieved at 24 h with  
1.0  $\mu\text{mol/l}$  cilostamide (2/24 oocytes, 8%,  $P < 0.01$ ) and 100  
 $\mu\text{mol/l}$  milrinone (2/32, 6%,  $P < 0.01$ ). In contrast, no significant  
difference in GVBD was noted between control oocytes and those  
incubated with up to 100  $\mu\text{mol/l}$  rolipram for 24 h (43/58, 74%) or  
48 h (44/58, 76%). Conclusions: These experiments establish the  
specificity and dose-dependent ability of PDE3, but not PDE4  
, inhibitors to block resumption of meiosis in macaque oocytes in  
vitro. Thus, PDE3 inhibitors have potential use as contraceptives in  
primates.

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ACCESSION NUMBER: 2002406331 EMBASE  
TITLE: Effect of vaginal sildenafil on the outcome  
of in vitro fertilization (IVF) after  
multiple IVF failures attributed to poor endometrial  
development.  
AUTHOR: Sher G.; Fisch J.D.  
CORPORATE SOURCE: Dr. G. Sher, 3121 S. Maryland Parkway, Las Vegas, NV  
89109, United States. gsher@sherinstitute.com  
SOURCE: Fertility and Sterility, (1 Nov 2002) Vol. 78, No. 5,  
pp. 1073-1076.  
Refs: 11  
ISSN: 0015-0282 CODEN: FESTAS  
PUBLISHER IDENT.: S 0015-0282(02)03375-7  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 010 Obstetrics and Gynecology  
030 Pharmacology  
037 Drug Literature Index

Searcher : Shears 571-272-2528

10/817312

LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20021202  
Last Updated on STN: 20021202

AB Objective: To evaluate the effects of vaginally administered **sildenafil** on endometrial thickness and IVF outcome in a large cohort of **infertile** women with poor endometrial development. Design: Retrospective cohort analysis. Setting: Private practice setting. Patient(s): A cohort of 105 **infertile** women aged <40 years, with normal ovarian reserve and at least two consecutive prior IVF failures attributed to inadequate endometrial development. Intervention(s): Patients underwent IVF using a long GnRH-a protocol with the addition of **sildenafil** vaginal suppositories (25 mg, 4 times per day) for 3-10 days. Main Outcome Measure(s): Peak endometrial development, pregnancy, and implantation rates. Result(s): Of 105 patients, 73 (70%; Group A), attained an endometrial thickness of  $\geq 9$  mm, whereas 32 (30%; Group B) did not. Implantation and ongoing pregnancy rates were significantly higher for Group A (29% and 45%) than for Group B (2% and 0). Of 11 women in Group B who had embryos transferred in that cycle, only one conception occurred, which resulted in a miscarriage. In Group B, 59% of women had a history of endometritis, compared with 44% in Group A. Conclusion(s): Vaginal administration of **sildenafil** enhanced endometrial development in 70% of patients studied. High implantation and ongoing pregnancy rates were achieved in a cohort with a poor prognosis for success. Previous endometritis may decrease the response to **sildenafil**. .COPYRG. 2002 by American Society for Reproductive Medicine.

L64 ANSWER 17 OF 56 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002127473 EMBASE  
TITLE: Benefit of vaginal **sildenafil** citrate in assisted reproduction therapy [1].  
AUTHOR: Paulus W.E.; Strehler E.; Zhang M.; Jelinkova L.; El-Danasouri I.; Sterzik K.  
CORPORATE SOURCE: Dr. W.E. Paulus, Christian-Lauritzen-Institut, Frauenstrasse 51, D-89073 Ulm, Germany. paulus@reprotox.de  
SOURCE: Fertility and Sterility, (2002) Vol. 77, No. 4, pp. 846-847.  
Refs: 7  
ISSN: 0015-0282 CODEN: FESTAS  
PUBLISHER IDENT.: S 0015-0282(01)03272-1  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Letter  
FILE SEGMENT: 010 Obstetrics and Gynecology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
ENTRY DATE: Entered STN: 20020418  
Last Updated on STN: 20020418

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L64 ANSWER 18 OF 56 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002449282 EMBASE  
TITLE: Treatment of gonadal damage in recipients of allogeneic or autologous transplantation for haematological

Searcher : Shears 571-272-2528



malignancies.

AUTHOR: Chatterjee R.; Kottaridis P.D.  
 CORPORATE SOURCE: Dr. R. Chatterjee, Reproductive Medicine Unit,  
 University College Hospital, EGA and Obstetric  
 Hospital, Huntley Street, London WC1E 6AU, United  
 Kingdom

SOURCE: Bone Marrow Transplantation, (2002) Vol. 30, No. 10,  
 pp. 629-635.  
 Refs: 58  
 ISSN: 0268-3369 CODEN: BMTRE

COUNTRY: United Kingdom  
 DOCUMENT TYPE: Journal; (Short Survey)  
 FILE SEGMENT: 003 Endocrinology  
 016 Cancer  
 025 Hematology  
 028 Urology and Nephrology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles

LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 ENTRY DATE: Entered STN: 20030103  
 Last Updated on STN: 20030103

AB Management of iatrogenic gonadal reproductive failure and sexual  
 morbidity assumes a priority, especially in young recipients of  
 high-dose chemotherapy and stem cell transplantation (SCT). Hormone  
 replacement treatment (HRT) is beneficial for correction of sexual  
 symptoms and osteoporosis in both sexes, especially in **females**  
 . Sperm banking is the standard technique for preservation of  
**fertility** in adult and sexually mature adolescent males.  
 Testicular tissue cryopreservation has a place in well-selected  
 azoospermic adults and in mentally and sexually competent adolescents.  
 In vitro **fertilisation** using superovulation with  
 embryo-cryopreservation (for future embryo transfer) is the most tried  
 method in **female** SCT recipients with good results. In  
 mentally and sexually competent adolescents and adults without a  
 partner, ovarian cortical tissue cryopreservation has a place for  
 subsequent re-implantation to orthotopic or heterotopic sites.  
 Gonadotrophin releasing hormone (GnRH) co-treatment during  
 chemotherapy, is a promising method for the future. Although  
 generally reassuring, continued monitoring of the offspring of SCT  
 survivors and follow-up of all recipients of SCT is important for  
 return of spontaneous or induced **fertility**.

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ACCESSION NUMBER: 2002335130 EMBASE  
 TITLE: The work has just begun for urologists: Highlights from  
 the 97th Annual Meeting of the American Urological  
 Association, Orlando, Florida, May 25-30, 2002.

AUTHOR: Susman E.  
 CORPORATE SOURCE: E. Susman, 3111 S. Dixie Highway, West Palm Beach, FL  
 33405, United States. edsusman@bellsouth.net

SOURCE: Drugs of Today, (2002) Vol. 38, No. 8, pp. 521-531,  
 Refs: 39  
 ISSN: 0025-7656 CODEN: MDACAP

COUNTRY: Spain  
 DOCUMENT TYPE: Journal; Conference Article  
 FILE SEGMENT: 028 Urology and Nephrology  
 030 Pharmacology

037 Drug Literature Index  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 20021003  
 Last Updated on STN: 20021003  
 DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L64 ANSWER 20 OF 56 MEDLINE on STN DUPLICATE 3  
 ACCESSION NUMBER: 2002211826 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11944932  
 TITLE: Differential effects of specific phosphodiesterase  
 isoenzyme inhibitors on bovine oocyte meiotic  
 maturation.  
 AUTHOR: Thomas Rebecca E; Armstrong David T; Gilchrist Robert B  
 CORPORATE SOURCE: Reproductive Medicine Unit, The University of Adelaide,  
 Adelaide, Australia.  
 SOURCE: Developmental biology, (2002 Apr 15) 244 (2) 215-25.  
 Journal code: 0372762. ISSN: 0012-1606.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200205  
 ENTRY DATE: Entered STN: 20020412  
 Last Updated on STN: 20020602  
 Entered Medline: 20020531

AB The differential regulation of cAMP levels within the oocyte and somatic (cumulus) cell compartments of the bovine follicle, and the subsequent regulation of oocyte meiotic maturation was examined through specific cell-type localisation of phosphodiesterases (PDEs). Selective PDE inhibitors were used to modulate cAMP levels in each of the two follicular compartments and to examine their effects on oocyte meiotic maturation. Ovaries were obtained from an abattoir and cumulus-oocyte complexes (COC) were aspirated from antral follicles into culture medium supplemented with 4 mg/ml BSA and 2mM 3-isobutyl-1-methylxanthine (IBMX). COC, denuded oocytes (DO), or mural granulosa cells (MGC) were cultured either with or without forskolin or FSH, in the presence of specific PDE inhibitors; either milrinone (PDE3 inhibitor), cilostamide (PDE3 inhibitor), or rolipram (PDE4 inhibitor). COC/DO cultures were assessed for meiotic progression and cAMP content, and MGC for cAMP production. The type 3 PDE inhibitor, but not the type 4, prevented spontaneous meiotic maturation and elevated intraoocyte cAMP in cultured denuded oocytes. In contrast, the type 4 PDE inhibitor had no effect on the oocyte, but elevated mural granulosa and cumulus cell cAMP production. The results of this study indicate that specific PDE subtypes are differentially localised within the two compartments of the bovine follicle-the type 3 PDE in the oocyte and the type 4 PDE in the granulosa cells. In addition, oocyte cAMP levels are primarily regulated in bovine oocytes by its degradation by PDE, whereas granulosa cell cAMP levels are controlled mainly by active adenylate cyclase, with both sources able to participate in oocyte meiotic regulation.  
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L64 ANSWER 21 OF 56 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN  
 ACCESSION NUMBER: 2002-097574 [13] WPIDS  
 DOC. NO. CPI: C2002-030375  
 TITLE: Use of substituted pyrazole compounds for treating  
 infertility, and new pyrazole compounds which

are luteinizing hormone and  
follicle stimulating  
hormone agonists.

DERWENT CLASS: B03  
INVENTOR(S): BRUGGER, N; EL TAYAR, N; JORAND-LEBRUN, C; REDDY, A  
P; SHROFF, H; DE LUCA, G  
PATENT ASSIGNEE(S): (SERO-N) SERONO REPRODUCTIVE BIOLOGY INST INC;  
(BRUG-I) BRUGGER N; (TAYA-I) EL TAYAR N; (JORA-I)  
JORAND-LEBRUN C; (REDD-I) REDDY A P; (SHRO-I) SHROFF  
H; (ISTF) ARS APPLIED RES SYSTEMS HOLDING NV  
COUNTRY COUNT: 96  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001087287	A2	20011122	(200213)*	EN	90
RW:	AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW				
	MZ NL OA PT SD SE SL SZ TR TZ UG ZW				
W:	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE				
	DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP				
	KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT				
	RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW				
AU 2001064694	A	20011126	(200222)		
US 2002132844	A1	20020919	(200264)		
EP 1282418	A2	20030212	(200312)	EN	
R:	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL				
	PT RO SE SI TR				
JP 2004501100	W	20040115	(200410)		168
US 2005026985	A1	20050203	(200511)		

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001087287	A2	WO 2001-US16189	20010519
AU 2001064694	A	AU 2001-64694	20010519
US 2002132844	A1 Provisional	US 2000-205814P	20000519
		US 2001-860658	20010519
EP 1282418	A2	EP 2001-939143	20010519
		WO 2001-US16189	20010519
JP 2004501100	W	JP 2001-583755	20010519
		WO 2001-US16189	20010519
US 2005026985	A1 Provisional	US 2000-205814P	20000519
	Cont of	US 2001-860658	20010519
		US 2004-921471	20040819

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001064694	A Based on	WO 2001087287
EP 1282418	A2 Based on	WO 2001087287
JP 2004501100	W Based on	WO 2001087287

PRIORITY APPLN. INFO: US 2000-205814P 20000519; US  
2001-860658 20010519; US  
2004-921471 20040819

AN 2002-097574 [13] WPIDS  
AB WO 200187287 A UPAB: 20021031

**NOVELTY** - The use of substituted pyrazole compounds (I) and (I') for treating **infertility** is new.

**DETAILED DESCRIPTION** - The use of a substituted pyrazole compound for treating **infertility**, or a disease or disorder associated with phosphodiesterase **PDE4**, adenosine transporters or prostanoid receptors, is new.

**INDEPENDENT CLAIMS** are included for the following:

- (1) new substituted pyrazole compounds of formula (I); and
- (2) compounds of formula (I').

**R1** = H; alkyl, alkenyl, alkynyl, carbocyclic aryl, aralkyl, heteroaromatic, heteroalicyclic, heteroaralkyl or heteroalicyclicalkyl, each optionally substituted;

**R2, R3** = H; halo; or alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carbocyclic aryl, aralkyl, heteroaromatic, heteroalicyclic, heteroaralkyl or heteroalicyclicalkyl, each optionally substituted;

**X** = alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, carbocyclic aryl, heteroaromatic, heteroalicyclic, heteroaralkyl or heteroalicyclicalkyl, each optionally substituted;

**Y** = optionally substituted amino; optionally substituted methylene; carbonyl; or sulfonyl;

**Z** = optionally substituted alkylamine; an amino acid; or a glycine;

**m, n** = 0 or 1;

**R1a, R2a, R3a** = H; or alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carbocyclic aryl, aralkyl, heteroaromatic, heteroalicyclic, heteroaralkyl or heteroalicyclicalkyl, each optionally substituted; and

**Xa** = alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, carbocyclic aryl, aralkyl, heteroaromatic, heteroalicyclic, heteroaralkyl or heteroalicyclicalkyl, each optionally substituted.

**ACTIVITY** - Antiinfertility.

**MECHANISM OF ACTION** - **Luteinizing hormone** agonists; **follicle stimulating hormone** agonists; phosphodiesterase **PDE4** inhibitor; adenosine transporter inhibitor; prostanoid receptor inhibitor.

In a test to determine **FSH** agonist activity, **N-(5-(1-(4-tert butylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl)hexanoyl)tyrosinamide** had **EC50 0.78 micro M**.

**USE** - For treating **infertility** in male and female mammals, e.g. a female with an **ovulatory** disorder, or being treated with an assisted reproduction procedure, or undergoing in-vitro **fertilization**; or a male with a spermatogenesis disorder.

The compounds may be administered in combination with other **fertility** agents, e.g. **follicle stimulating hormone** and/or **luteinizing hormone**, such as **Gonal-F** or **Pergonal**.

**ADVANTAGE** - The pyrazole compounds can be administered orally, and without extensive medical specialist supervision, unlike current protein therapeutics, e.g. **Follicle Stimulating Hormone**.

Dwg. 0/0

10/817312

TITLE: New agents for the medical treatment of interstitial cystitis.  
AUTHOR: Theoharides T.C.; Sant G.R.  
CORPORATE SOURCE: T.C. Theoharides, Dept. of Pharmacology/Exp. Therap., Internal Medicine, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, United States. theoharis.theoharides@tufts.edu  
SOURCE: Expert Opinion on Investigational Drugs, (2001) Vol. 10, No. 3, pp. 521-546.  
Refs: 234  
ISSN: 1354-3784 CODEN: EOIDER  
COUNTRY: United Kingdom  
DOCUMENT TYPE: Journal; General Review  
FILE SEGMENT: 008 Neurology and Neurosurgery  
028 Urology and Nephrology  
030 Pharmacology  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20010322  
Last Updated on STN: 20010322

AB Interstitial cystitis (IC) is a painful, **sterile**, disorder of the urinary bladder characterised by urgency, frequency, nocturia and pain. IC occurs primarily in women but also in men with recent findings indicating that chronic, abacterial prostatitis may be a variant of this condition. The prevalence of IC has ranged from about 8-60 cases/100,000 **female** patients depending on the population evaluated. About 10% of patients have severe symptoms that are associated with Hunner's ulcers on bladder biopsy; the rest could be grouped in those with or without bladder inflammation. Symptoms of IC are exacerbated by stress, certain foods and **ovulatory** hormones. Many patients also experience allergies, irritable bowel syndrome (IBS) and migraines. There have been various reports indicating dysfunction of the bladder glycosaminoglycan (GAG) protective layer and many publications showing a high number of activated bladder mast cells. Increasing evidence suggests that neurogenic inflammation and/or neuropathic pain is a major component of IC pathophysiology. Approved treatments so far include intravesical administration of dimethylsulphoxide (DMSO) or oral pentosanpolysulphate (PPS). New treatments focus on the combined use of drugs that modulate bladder sensory nerve stimulation (neurolytic agents), inhibit neurogenic activation of mast cells, or provide urothelial cytoprotection, together with new drugs with anti-inflammatory activity.

L64 ANSWER 23 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:178297 BIOSIS  
DOCUMENT NUMBER: PREV200200178297  
TITLE: New treatment for Asherman's syndrome: Vaginal **sildenafil** (Viagra).  
AUTHOR(S): Saroufim, P. [Reprint author]; Jaoude, I. A. [Reprint author]  
CORPORATE SOURCE: Center for Reproductive Medicine, Abou Jaoude Hospital, Jaleldib, Lebanon  
SOURCE: Human Reproduction (Oxford), (2001) Vol. 16, No. Abstract Book 1, pp. 177. print.  
Meeting Info.: 17th Annual Meeting of the European

Searcher : Shears 571-272-2528

10/817312

Society of Human Reproduction and Embryology. Lausanne, Switzerland. July 01-04, 2001. European Society of Human Reproduction and Embryology; European Society of Human Reproduction and Embryology.  
CODEN: HUREEE. ISSN: 0268-1161.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 6 Mar 2002  
Last Updated on STN: 6 Mar 2002

L64 ANSWER 24 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation  
on STN

ACCESSION NUMBER: 2002:165815 BIOSIS  
DOCUMENT NUMBER: PREV200200165815  
TITLE: Benefit of vaginal **sildenafil** in assisted reproduction therapy.

AUTHOR(S): Paulus, W. E. [Reprint author]; Strehler, E. [Reprint author]; Zhang, M. [Reprint author]; Jelinkova, L. [Reprint author]; Sterzik, K. [Reprint author]

CORPORATE SOURCE: Christian-Lauritzen-Institut, Frauenstrasse 56, D-89073, Ulm, Germany

SOURCE: Human Reproduction (Oxford), (2001) Vol. 16, No. Abstract Book 1, pp. 116-117. print.  
Meeting Info.: 17th Annual Meeting of the European Society of Human Reproduction and Embryology. Lausanne, Switzerland. July 01-04, 2001. European Society of Human Reproduction and Embryology; European Society of Human Reproduction and Embryology.  
CODEN: HUREEE. ISSN: 0268-1161.

DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Mar 2002  
Last Updated on STN: 4 Apr 2002

L64 ANSWER 25 OF 56 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS  
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ACCESSION NUMBER: 2001140243 EMBASE  
TITLE: **Fertility** and sexual life of men after their forties and in older age.

AUTHOR: Schill W.-B.

CORPORATE SOURCE: Prof. W.-B. Schill, Department of Dermatology/Andrology, Justus Liebig University, Gaffkystr. 14, 35385 Giessen, Germany.  
Wolf-Bernhard.Schill@derma.med.uni-giessen.de

SOURCE: Asian Journal of Andrology, (2001) Vol. 3, No. 1, pp. 1-7.  
Refs: 33  
ISSN: 1008-682X CODEN: ASJAF8

COUNTRY: China

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology  
017 Public Health, Social Medicine and Epidemiology  
020 Gerontology and Geriatrics  
028 Urology and Nephrology  
037 Drug Literature Index  
038 Adverse Reactions Titles

Searcher : Shears 571-272-2528

10/817312

LANGUAGE: English  
SUMMARY LANGUAGE: English  
ENTRY DATE: Entered STN: 20010430  
Last Updated on STN: 20010430

AB Owing to the demographic development, the aging male will require more consideration in future. In contrast to a rapid decline of estradiol during menopause in women, the process of aging in the male is retarded and subject to high individual variations. Impairment of spermatogenesis is observed as a continuous process occurring over decades. However, only about 50% of men in their eighties show complete loss of **fertility**. In principle, spermatogenesis may be retained well into senescence. Of importance for the individual health condition is the fact that the number of Leydig cells declines with advancing age. Thus, altered sex hormone concentrations in aging men result from both functional disturbances and a gradual reduction in Leydig cells. Furthermore, an impaired feed-back mechanism of the pituitary-gonadal axis occurs, with disappearance of the circadian testosterone (T) rhythm. **LH** and **FSH** levels are increased, and a reduced bioavailability of sex hormones is observed. Lower total testosterone concentrations in men over 60 years are accompanied by clinical signs of reduced virility, such as decreased muscle mass and strength as well as reduced sexual hair growth and libido. An age-related decline in androgen secretion and plasma testosterone levels therefore suggests the use of androgen supplementation. However, there is a lack of risk-benefit long-term studies. Increased research in the male is mandatory to meet the requirements of the aging population. This should include the availability of precise epidemiological data about the frequency of partial androgen deficiency in aging males (PADAM).

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on STN DUPLICATE 4

ACCESSION NUMBER: 2000:231391 BIOSIS  
DOCUMENT NUMBER: PREV200000231391  
TITLE: Vaginal **sildenafil** (Viagra): A preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF.  
AUTHOR(S): Sher, Geoffrey [Reprint author]; Fisch, Jeffrey D.  
CORPORATE SOURCE: Sher Institute for Reproductive Medicine, 3121 S. Maryland Parkway, Suite 300, Las Vegas, NV, 89109, USA  
SOURCE: Human Reproduction (Oxford), (April, 2000) Vol. 15, No. 4, pp. 806-809. print.  
CODEN: HUREEE. ISSN: 0268-1161.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 7 Jun 2000  
Last Updated on STN: 5 Jan 2002

AB Endometrial growth is thought to depend on uterine artery blood flow and the importance of endometrial development on in-vitro **fertilization** (IVF) outcome has been previously reported. Nitric oxide (NO) relaxes vascular smooth muscle through a cGMP-mediated pathway and NO synthase isoforms have been identified in the uterus. **Sildenafil** citrate (Viagra), a type 5-specific phosphodiesterase inhibitor, augments the vasodilatory effects of NO by preventing the degradation of cGMP. In this preliminary report we describe the use of vaginal **sildenafil** to improve uterine artery blood flow and sonographic endometrial appearance in four patients with prior failed assisted reproductive cycles due to poor

endometrial response. The uterine artery pulsatility index (PI) was measured in a mock cycle after pituitary down-regulation with Lupron. The PI was decreased after 7 days of **sildenafil** (indicating increased blood flow) and returned to baseline following treatment with placebo. The combination of **sildenafil** and oestradiol valerate improved blood flow and endometrial thickness in all patients. These findings were reproduced in an ensuing gonadotrophin-stimulated cycle. Three of the four patients conceived. Although greater numbers of patients and randomized evaluation are needed to validate this treatment, vaginal **sildenafil** may be effective for improving uterine artery blood flow and endometrial development in IVF patients with prior poor endometrial response.

L64 ANSWER 27 OF 56 MEDLINE on STN DUPLICATE 5  
 ACCESSION NUMBER: 97179080 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9027367  
 TITLE: Src tyrosine kinase activity in rat thecal-interstitial cells and mouse TM3 Leydig cells is positively associated with cAMP-specific phosphodiesterase activity.  
 AUTHOR: Taylor C C; Limback D; Terranova P F  
 CORPORATE SOURCE: Department of Physiology, University of Kansas Medical Center, Kansas City 66160-7401, USA.  
 CONTRACT NUMBER: CA 50616 (NCI)  
 HD 33994 (NICHD)  
 SOURCE: Molecular and cellular endocrinology, (1997 Jan 3) 126 (1) 91-100.  
 Journal code: 7500844. ISSN: 0303-7207.  
 PUB. COUNTRY: Ireland  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199704  
 ENTRY DATE: Entered STN: 19970424  
 Last Updated on STN: 20000303  
 Entered Medline: 19970417

AB Phosphodiesterases (PDEs) play a critical role in the regulation of intracellular cyclic nucleotide concentration and, consequently, regulate the state of cellular differentiation. We have reported that the Src-selective tyrosine kinase inhibitor, herbimycin A, potentiates **luteinizing hormone (LH)-stimulated** cAMP accumulation in culture media by **ovarian** thecal-interstitial cells (TIC; see Taylor, C and Terranova, P.F. (1995) Lipopolysaccharide inhibits rat **ovarian** thecal-interstitial cell steroid secretion in vitro. Endocrinology 136, 5527-5532). The present study was conducted to investigate the effects of herbimycin, and changes in Src tyrosine kinase activity, on PDE activity in rat TIC and in the mouse TM3 Leydig cell line. Treatment of TIC with herbimycin (1 microM) for 24 h inhibited basal and LH-stimulated PDE activity (approximately 50 and 70%, respectively) and was associated with an increase in cAMP and progesterone accumulation in culture media. Treatment of TM3 cells with herbimycin inhibited PDE activity and increased cAMP accumulation in a dose- and time-dependent manner. TM3 cell cultures challenged with herbimycin had lower Src tyrosine kinase activity than controls (approximately 50%); however, protein kinase A activity was unaffected. TM3 cells stably transfected with a dominant negative Src tyrosine kinase (TM3SrcK-) had lower PDE activity than cells transfected with a G418 resistance gene alone (TM3pSV2neo) which



served as control cells. Conversely, TM3 cells expressing a temperature-sensitive Src kinase had significantly greater PDE activity at the Src active temperature (35 degrees C; the temperature at which the enzyme is active) than TM3pSV2neo control cells grown at the same temperature. TM3 cell lysates hydrolyzed minimal amounts of cGMP, indicating a cAMP-specific PDE. Phosphodiesterase activity in both TM3 and rat TIC was sensitive to the PDE4-selective inhibitor RO20-1724, indicating the predominant active enzyme is probably a member of the cAMP-specific PDE4 family. From the present data, we conclude that a tyrosine kinase of the Src family may play an important role in regulating phosphodiesterase activity in thecal and Leydig cells, and thus regulate intracellular cAMP and the state of cellular differentiation.

L64 ANSWER 28 OF 56 MEDLINE on STN DUPLICATE 6  
 ACCESSION NUMBER: 96427392 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 8812137  
 TITLE: Oocyte maturation involves compartmentalization and opposing changes of cAMP levels in follicular somatic and germ cells: studies using selective phosphodiesterase inhibitors.  
 AUTHOR: Tsafiriri A; Chun S Y; Zhang R; Hsueh A J; Conti M  
 CORPORATE SOURCE: Department of Obstetrics and Gynecology, Stanford University School of Medicine, California 94305-5317, USA.  
 CONTRACT NUMBER: HD20788 (NICHD)  
 HD31566 (NICHD)  
 SOURCE: Developmental biology, (1996 Sep 15) 178 (2) 393-402.  
 Journal code: 0372762. ISSN: 0012-1606.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199612  
 ENTRY DATE: Entered STN: 19970128  
 Last Updated on STN: 20000303  
 Entered Medline: 19961210  
 AB The second messenger cAMP has been implicated in the regulation of mammalian and amphibian oocyte maturation. Although a decrease in intraoocyte levels of cAMP precedes germinal vesicle breakdown (GVBD), the gonadotropin induction of ovulation and oocyte maturation is associated with major increases of cAMP in ovarian follicles. In the mammalian system, isolated oocytes undergo spontaneous maturation in vitro but this process is blocked by treatment with a phosphodiesterase (PDE) inhibitor, IBMX, which increases intraoocyte cAMP levels. In contrast, the same inhibitor, when added to cultured follicles for a brief time, increases follicle cAMP levels, followed by the induction of GVBD. To resolve the paradoxical actions of this PDE inhibitor on the maturation of isolated and follicle-enclosed oocytes, we hypothesized that meiotic maturation requires opposing fluctuations of cAMP levels in the somatic granulosa and germ cells. Such opposing fluctuations may result from selective expression and regulation of PDEs in the somatic and germ cell compartments of the follicle. To test this hypothesis, PDE activity was manipulated in different follicular cells using type-specific inhibitors. The impact of the ensuing changes in cAMP levels in the two compartments was monitored by the induction of GVBD. In isolated oocytes, spontaneous GVBD was blocked by two inhibitors of type 3 PDE (cGMP-inhibited: CGI-PDE), milrinone and cilostamide. In

contrast, treatment with an inhibitor for type 4 PDE (cAMP-specific), rolipram, was ineffective. These findings suggest that the oocyte expresses type 3 but not type 4 PDE and that increases in intraoocyte cAMP suppress GVBD. This hypothesis was confirmed by in situ hybridization studies with PDE3 and PDE4 probes. PDE3B mRNA was concentrated in oocytes while PDE4D was mainly expressed in granulosa cells. In cultured follicles, LH treatment induced oocyte maturation but the gonadotropin action was blocked by inhibitors of type 3 but not the type 4 PDE inhibitors. Furthermore, treatment with the type 4, but not the type 3, PDE inhibitor mimics the action of LH and induces oocyte maturation, presumably by increasing cAMP levels in granulosa cells. Our findings indicate that PDE subtypes 4 and 3 are located in follicle somatic and germ cells, respectively. Preferential inhibition of PDE 3 in the oocyte may lead to a delay in oocyte maturation without affecting the cAMP-induced ovulatory process in the somatic cells. Conversely, selective suppression of granulosa cell cAMP-PDE may enhance the gonadotropin induction of ovulation and oocyte maturation. Thus, in addition to the well-recognized differential expression and regulation of adenylate cyclase in the somatic and germ cell compartments of the follicle, we suggest that selective regulation and expression of PDEs may be involved in the regulation of cAMP levels and control of oocyte maturation in the preovulatory mammalian follicle.

L64 ANSWER 29 OF 56 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96027413 EMBASE  
DOCUMENT NUMBER: 1996027413  
TITLE: [Deep venous thrombosis and in vitro fecondation about 1 case].  
THROMBOSE VEINEUSE PROFONDE ET FECONDATION IN VITRO: A PROPOS D'UN CAS.

AUTHOR: Laprevote-Heully M.C.; Schmidt C.; Briquel M.E.; Guillet-May F.; Larcen A.

SOURCE: Annales Medicales de Nancy et de l'Est, (1995) Vol. 34, No. 5-6, pp. 297-299.  
ISSN: 0221-3796 CODEN: AMNADI

COUNTRY: France  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 003 Endocrinology  
005 General Pathology and Pathological Anatomy  
010 Obstetrics and Gynecology  
018 Cardiovascular Diseases and Cardiovascular Surgery  
025 Hematology  
037 Drug Literature Index  
038 Adverse Reactions Titles

LANGUAGE: French  
SUMMARY LANGUAGE: French; English  
ENTRY DATE: Entered STN: 960212  
Last Updated on STN: 960212

AB One case of venous cervico-thoracic thrombosis following ovarian hyperstimulation with induction treatment before FIV is reported in a young woman (37 years old), with important smoking and administration of oestrogen-progestagen contraceptives during 10 years. The venous thrombosis occurred early at 6 weeks of gestation. The etiologic check-up evidenced a costo-clavicular clip. This observation confirm the thrombogenic effects of ovulation

treatment who also managed to hemodynamic (Doppler) monitoring and heparin prevention when an ovarian hyperstimulation developed biologic modifications on clotting.

L64 ANSWER 30 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation  
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ACCESSION NUMBER: 1989:71834 BIOSIS  
DOCUMENT NUMBER: PREV198987036232; BA87:36232  
TITLE: THE EFFECTS OF FSH AND CYCLIC GMP ON CYCLIC  
AMP-PHOSPHODIESTERASE AND RESUMPTION OF MEIOSIS IN  
HAMSTER CUMULUS-OOCYTE COMPLEXES.  
AUTHOR(S): HUBBARD C J [Reprint author]; PRICE J  
CORPORATE SOURCE: DEP BIOL SCI, NORTHERN ILLINOIS UNIV, DEKALB, ILL  
60115, USA  
SOURCE: Biology of Reproduction, (1988) Vol. 39, No. 4, pp.  
829-838.  
CODEN: BIREBV. ISSN: 0006-3363.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
ENTRY DATE: Entered STN: 23 Jan 1989  
Last Updated on STN: 23 Jan 1989

AB The effects of cGMP on spontaneous oocyte maturation and cAMP-PDE on spontaneous oocyte maturation and cyclic adenosine 3',5'-eumulus monophosphate phosphodiesterase activity (cAMP-PDE) were evaluated by using cumulus-oocyte complex (COCs) from proestrous hamsters. After a 2-h incubation period, FSH (10 µg/ml and 1 µg/ml) reduced the percentage of maturing oocytes compared with controls. This inhibition was partially overcome when cGMP-elevating agents (8-Bromo-cGMP, atrial natriuretic factor or sodium nitroprusside) were included with FSH. After a 3-h period, incubation with FSH and cGMP-elevating agents alone increased the maturation rate above that of the controls. The acceleration effects of cGMP on the maturation rate appear to be caused by its capacity to lower cAMP levels. Combining FSH (1 µg/ml) with sodium nitroprusside reduced cAMP levels in COCs (not oocytes) compared with groups exposed to FSH alone. FSH increased cGMP levels in COCs in a dose- and time-dependent manner. Both FSH and cGMP-elevating agents produced a dose-dependent increased cAMP-PDE activity in COCs (not oocytes) following a 2-h incubation period. Together, these results suggest that, in vivo, FSH stimulates a rise in both cAMP and cGMP in COCs. While the increase in cAMP may be the initial meiotic trigger, cGMP may serve to subsequently lower cAMP by activating cAMP-PDE and thus permit the maturational process to continue.

L64 ANSWER 31 OF 56 MEDLINE on STN DUPLICATE 7  
ACCESSION NUMBER: 88082472 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2826114  
TITLE: Adenosine receptor-mediated effects by nonmetabolizable adenosine analogs in preovulatory rat granulosa cells: a putative local regulatory role of adenosine in the ovary.  
AUTHOR: Billig H; Thelander H; Rosberg S  
CORPORATE SOURCE: Department of Physiology, University of Goteborg, Sweden.  
SOURCE: Endocrinology, (1988 Jan) 122 (1) 52-61.  
Journal code: 0375040. ISSN: 0013-7227.  
PUB. COUNTRY: United States

10/817312

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 198802  
ENTRY DATE: Entered STN: 19900305  
Last Updated on STN: 19980206  
Entered Medline: 19880203

AB The influence of nonmetabolizable adenosine analogs on cAMP production was investigated in preovulatory rat granulosa cells. 5'-(N-ethyl)Carboxamido-adenosine (NECA), a stimulatory A2-adenosine receptor agonist, stimulated cAMP accumulation, and NECA and 2-chloro-adenosine also potentiated the response to FSH. The adenosine receptor antagonist 8-phenyltheophylline antagonized the effect of NECA, shown by a shift in the dose-response curve to the right. The **stimulatory** effect of NECA was also seen in an **ovarian** membrane preparation, where NECA **stimulated** adenylate cyclase in both the presence and absence of FSH. The stimulatory effect of NECA was also decreased by 8-phenyltheophylline in this preparation. The A1-receptor agonists N6-(R-phenyl-isopropyl)-adenosine (R-PIA) and N6-(S-phenyl-isopropyl)-adenosine (S-PIA) both inhibited FSH-stimulated cAMP accumulation. The inhibitory effects of R-PIA and S-PIA, but not the stimulatory effects of NECA, could be counteracted by **dipyridamole**, a nucleoside transport inhibitor. Furthermore, R-PIA and S-PIA inhibited adenosine uptake into granulosa cells. Thus, the inhibitory effects of R-PIA and S-PIA are not likely to be mediated via membrane-bound inhibitory A1-adenosine receptors. Neither the stimulatory effects of NECA nor the inhibitory effects of R- and S-PIA could be attributed to changes in ATP levels, since the ATP levels were unaffected by these analogs. The results of this study indicate the existence of stimulatory A2-adenosine receptors in preovulatory rat granulosa cells and suggest a membrane-associated modulatory role of adenosine in preovulatory granulosa cells.

L64 ANSWER 32 OF 56 MEDLINE on STN DUPLICATE 8  
ACCESSION NUMBER: 86234268 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 3086937  
TITLE: Prostacyclin and steroidogenesis in goat ovarian cell types in vitro.  
AUTHOR: Band V; Kharbanda S M; Murugesan K; Farooq A  
SOURCE: Prostaglandins, (1986 Mar) 31 (3) 509-25.  
Journal code: 0320271. ISSN: 0090-6980.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198607  
ENTRY DATE: Entered STN: 19900321  
Last Updated on STN: 19900321  
Entered Medline: 19860702

AB Granulosa, theca and corpus luteum cells of the goat ovary were isolated and incubated separately for 6 hours, with or without various modulators. Arachidonic acid (AA, 10 ng to 100 micrograms/ml), the precursor for prostaglandin synthesis, produced a dose-dependent increase in progesterone (P4) and estradiol-17 beta (E2) production by all the cell types. Prostaglandin synthetase inhibitors, aspirin (10(-6)-10(-3)M) and indomethacin (100 ng-1 mg/ml), produced a dose-dependent decrease in arachidonic acid-stimulated (100 micrograms/ml) steroid production. Prostacyclin synthetase

Searcher : Shears 571-272-2528

stimulators, trapidil (1.6 micrograms- 1 mg/ml) and **dipyridamole** (10(-6)-10(-3)M), when added alone or along with AA, did not affect steroid production. Up to 100 micrograms/ml of U-51605 (9,11-azoprostanoic acid), a prostacyclin synthetase inhibitor, did not inhibit basal or AA-stimulated steroid production. Prostacyclin (PGI<sub>2</sub>) and its stable analog 6 beta PGI<sub>1</sub> (0.01-10 micrograms/ml) produced a dose-dependent increase in P<sub>4</sub> and E<sub>2</sub> production in all the three cell types. Increase at 1 and 10 micrograms/ml was significant in all cases. 6-keto-PGE<sub>1</sub> (an active metabolite of PGI<sub>2</sub> in certain systems) produced an increase in steroid production which was significant in theca at greater than or equal to 1 microgram/ml concentrations but had no significant effect on granulosa and corpus luteum cells at any dose level. 6-keto-PGF<sub>1</sub> alpha (stable metabolite of PGI<sub>2</sub>) was without effect in the present system. The lack of effect of PGI<sub>2</sub> at lower concentrations was not altered by either differentiation of the cells with **FSH** and testosterone or addition of steroid precursors, testosterone and pregnenolone. The present results indicate that AA-stimulated steroid production in the goat **ovarian** cell type is mediated by prostaglandins other than PGI<sub>2</sub> though PGI<sub>2</sub> itself can positively modulate the steroid production.

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ACCESSION NUMBER: 1985:415252 BIOSIS  
DOCUMENT NUMBER: PREV198580085244; BA80:85244  
TITLE: REGULATION OF APOLIPOPROTEIN E SYNTHESIS IN RAT OVARIAN GRANULOSA CELLS.  
AUTHOR(S): DRISCOLL D M [Reprint author]; SCHREIBER J R; SCHMIT V M; GETZ G S  
CORPORATE SOURCE: DEP PATHOL, UNIV CHICAGO, CHICAGO, ILL 60637, USA  
SOURCE: Journal of Biological Chemistry, (1985) Vol. 260, No. 15, pp. 9031-9038.  
CODEN: JBCHA3. ISSN: 0021-9258.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB Apoprotein E (apo-E) is a surface component of several classes of plasma lipoproteins. It functions as a ligand for receptor-mediated uptake of lipoproteins. Granulosa cells from **ovaries** of diethylstilbestrol-stimulated hypophysectomized immature rats cultured in serum-free medium with [35S]methionine secrete a 34-kDa [kilodalton] protein which reacts with a monospecific anti-rat apo-E antibody and represents 0.2% of total secreted protein. Protease mapping confirms that this protein is apoprotein E. The secreted apoprotein E may be complexed with lipid since it floats in the ultracentrifuge at density < 1.21 µg/ml. Freshly isolated granulosa cells contain receptors for **FSH** but not for human **chorionic gonadotropin** (hCG) or prolactin. Apoprotein E secretion is stimulated 2-fold by **FSH**, but hCG and prolactin have no effect. When granulosa cells develop hCG and prolactin receptors after 48 h of culture with **FSH**, apoprotein E secretion is not stimulated by addition of **FSH**, hCG, or prolactin although steroidogenesis is induced. The addition of 10<sup>-7</sup> M androgen plus **FSH** stimulates a marked increase in progesterone synthesis over **FSH** alone, but androgen has little added effect on apoprotein E secretion. Cholera toxin (1.25 µg/ml) and dibutyryl cAMP (5 mg/ml), both of which increase intracellular cAMP, stimulate apo-E secretion 9-fold

and 12-fold, respectively. The dibutyryl cAMP effect is dependent on both dose ( $\geq 0.5$  mg/ml required) and time (onset of 24 h, maximum at 48 h, and back to near baseline at 96 h). Isobutylmethylxanthine, a phosphodiesterase inhibitor, augments FSH-stimulated apoprotein E synthesis 2.5-fold, supporting a role for cAMP in mediating the FSH effect. This is the first demonstration of the hormonal regulation of apoprotein E synthesis in an extrahepatic tissue.

L64 ANSWER 34 OF 56 MEDLINE on STN  
 ACCESSION NUMBER: 86104529 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 3936553  
 TITLE: Gonadotropin-induced inhibition of oxygen consumption in rat oocyte-cumulus complexes: relief by adenosine.  
 AUTHOR: Billig H; Magnusson C  
 SOURCE: Biology of reproduction, (1985 Nov) 33 (4) 890-8.  
 Journal code: 0207224. ISSN: 0006-3363.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198603  
 ENTRY DATE: Entered STN: 19900321  
 Last Updated on STN: 19970203  
 Entered Medline: 19860310

AB In the cumulus-oocyte complex (COC), as well as in the whole ovarian follicle, gonadotropins stimulate glycolysis, measured as lactate accumulation. In contrast to this, COC oxygen consumption is decreased by gonadotropins. One possible explanation for this inhibition is a competition for a limited supply of cofactors, common for both the glycolytic pathway and the respiratory chain. In the present study, addition of adenosine to COCs cultured with gonadotropins restored the oxygen consumption to basal levels. This effect was specific for metabolizable adenosine. Other nucleosides or non-metabolizable 2-chloro-adenosine had no effect. Adenosine also increased ATP and decreased lactate accumulation by the COC. The nucleoside transport inhibitor dipyridamol abolished the effects of adenosine on oxygen consumption and ATP accumulation. Taken together, these results support the hypothesis that a relative lack of adenosine-derived cofactors is probably involved in the decrease of oxygen consumption in vitro by gonadotropin-stimulated cumulus cells.

L64 ANSWER 35 OF 56 MEDLINE on STN DUPLICATE 9  
 ACCESSION NUMBER: 85230427 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 2988917  
 TITLE: Adenosine differentially amplifies luteinizing hormone- over follicle-stimulating hormone-mediated effects in acute cultures of rat granulosa cells.  
 AUTHOR: Ohkawa R; Polan M L; Behrman H R  
 CONTRACT NUMBER: HD-05927 (NICHD)  
 HD-10718 (NICHD)  
 SOURCE: Endocrinology, (1985 Jul) 117 (1) 248-54.  
 Journal code: 0375040. ISSN: 0013-7227.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

10/817312

ENTRY MONTH: 198508  
ENTRY DATE: Entered STN: 19900320  
Last Updated on STN: 19970203  
Entered Medline: 19850802

AB Adenosine has been shown to acutely amplify **LH**-dependent events in luteal cells and **FSH**-dependent events in granulosa cells. In this study, the specificity of purines on mature rat granulosa cell ATP levels in short term culture was assessed, and a comparison of the relative effect of adenosine on amplification of **FSH**- and **LH**-stimulated cAMP accumulation was made. Adenosine rapidly and significantly increased ATP levels in granulosa cells. This effect was maximal (approximately 2-fold) within 60 min of culture and occurred in the absence or presence of **FSH** or **LH**. The increase in granulosa cell ATP levels by adenosine was dose dependent, with half-maximal and maximum responses of 10 and 30 microM adenosine, respectively. **Dipyridamole** (10 microM), a purine transport inhibitor, blocked the adenosine-dependent increase in granulosa cell ATP levels. Adenosine and 5'-AMP were equipotent in increasing cell ATP levels; adenine also increased ATP levels, but was significantly less active (approximately 50% of adenosine), whereas hypoxanthine, inosine, and xanthine were inactive. **FSH** was consistently found to decrease granulosa cell ATP levels by about 30% in the absence or presence of adenosine, whereas **LH** had no effect on cell levels of ATP. Both **FSH** and **LH** significantly stimulated cAMP accumulation in granulosa cells, but the maximal response to **FSH** was substantially greater than that to **LH**. Adenosine significantly amplified cAMP accumulation in response to both **FSH** and **LH**, but the effect of adenosine on this response to **FSH** was modest. Amplification by adenosine of cAMP accumulation in response to **LH** was substantial and about 2- to 3-fold greater than that seen with **FSH**. These studies show that purines acutely and specifically increase ATP levels in rat granulosa cells. Since adenosine augments **LH**-dependent cAMP accumulation to a greater extent than **FSH**-stimulated cAMP production, we suggest that adenosine may favor premature follicular luteinization and, perhaps, function as a mediator of atresia in the developing follicle.

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ACCESSION NUMBER: 1985:356549 BIOSIS  
DOCUMENT NUMBER: PREV198580026541; BA80:26541  
TITLE: IN-VITRO STUDIES ON OVULATORY MECHANISMS IN  
THE HEN.  
AUTHOR(S): MOUDGAL R P [Reprint author]; RAZDAN M N  
CORPORATE SOURCE: DEP ANIMAL PRODUCTION PHYSIOL, HARYANA AGRIC UNIV,  
HISSAR-12500, INDIA  
SOURCE: Zentralblatt fuer Veterinaermedizin Reihe A, (1985)  
Vol. 32, No. 3, pp. 179-184.  
ISSN: 0721-0981.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB The addition of an extract from the largest ovarian follicles of hens (.apprx. 0.5 h prior to expected ovulation) to the incubation medium induced in vitro follicular ovulation in follicles removed 20-24 h prior to expected ovulation. An extract from immature (next to largest) follicles inhibited the

Searcher : Shears 571-272-2528

**ovulatory** effect of **LH** [**luteinizing hormone**] in quantities normally sufficient to cause **ovulation** in vitro. **Ovulation** in such cases could be brought about only by changing the medium with a higher concentration of **LH**, thereby indicating the presence of some dose-dependent **ovulation** inhibitory mechanism in the immature ovarian follicle or some facilitatory mechanism developing in the largest follicle prior to **ovulation**, an indication that both these mechanisms are working. **LH** or adrenaline [epinephrine] alone or in combination with imidazol (phosphodiesterase stimulator which inactivates cAMP) or tolazoline ( $\alpha$ -adrenergic receptor blocker) were tested in different incubation media. Follicles were incubated at 41° C for .apprx. 10 h to observe the induction of in vitro **ovulation**. Evidently, the **LH ovulatory** effect is mediated through cAMP and is facilitated by  $\alpha$ -adrenergic receptors, while adrenaline involvement in **ovulation** acts through  $\alpha$ -adrenergic receptors without involving cAMP.

L64 ANSWER 37 OF 56 MEDLINE on STN DUPLICATE 10  
 ACCESSION NUMBER: 84232328 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 6203565  
 TITLE: Inhibitory actions of adenosine on **follicle-stimulating hormone**-induced differentiation of cultured rat granulosa cells.  
 AUTHOR: Knecht M; Darbon J M; Ranta T; Baukal A; Catt K J  
 SOURCE: Biology of reproduction, (1984 Jun) 30 (5) 1082-90.  
 Journal code: 0207224. ISSN: 0006-3363.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198408  
 ENTRY DATE: Entered STN: 19900320  
 Last Updated on STN: 19900320  
 Entered Medline: 19840820

AB To determine the effects of adenosine on **follicle-stimulating hormone** (FSH)-induced differentiation, granulosa cells isolated from the ovaries of diethylstilbestrol-treated immature rats were cultured with increasing concentrations of the nucleoside and modulators of adenosine action. Although adenosine had no effect on basal granulosa cell function during 48 h of culture, concentrations of the nucleoside from 10 microM to 1 mM progressively inhibited FSH-induced responses, including progesterone production and expression of FSH and luteinizing hormone (LH) receptors. Adenosine had biphasic effects on FSH-stimulated cAMP accumulation, causing inhibition of cAMP production at 10 to 100 microM and stimulation at higher concentrations. The enhancement of cAMP production by 1 mM adenosine occurred during the first 24 h of culture, while both 100 microM and 1 mM adenosine reduced FSH-stimulated cAMP production from 24 to 48 h. The inhibitory effects of adenosine were prevented by adenosine deaminase and dipyridamole, an inhibitor of adenosine transport, and were antagonized by 1-methyl-3-isobutylxanthine. The inhibition of cAMP and progesterone production by adenosine was partially overcome when cells were washed and reincubated with forskolin, but not with FSH. Adenine, guanosine, and inosine at concentrations of 100 microM did not modify FSH-induced cAMP formation or



**LH** receptor induction. These results indicate that adenosine exerts predominantly inhibitory actions on hormone-induced granulosa cell differentiation, as manifested by prominent reductions in steroidogenesis and gonadotropin receptor expression.

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on STN DUPLICATE 11

ACCESSION NUMBER: 1984:338302 BIOSIS  
DOCUMENT NUMBER: PREV198478074782; BA78:74782  
TITLE: CYCLIC GMP PHOSPHO DI ESTERASE AND GUANYLATE CYCLASE  
ACTIVITIES IN RABBIT OVARIES AND THE EFFECT  
OF IN-VIVO STIMULATION WITH  
LUTEINIZING HORMONE.

AUTHOR(S): PATWARDHAN V V [Reprint author]; LANTHIER A  
CORPORATE SOURCE: LABORATORIE D'ENDOCRINOLOGIE, HOPITAL NOTRE-DAME,  
UNIVERSITE DE MONTREAL, MONTREAL, QUEBEC H2L 4K8,  
CANADA

SOURCE: Journal of Endocrinology, (1984) Vol. 101, No. 3, pp.  
305-310.

CODEN: JOENAK. ISSN: 0022-0795.

DOCUMENT TYPE: Article

FILE SEGMENT: BA

LANGUAGE: ENGLISH

AB The activities of guanylate cyclase and cGMP phosphodiesterase, enzymes that are responsible for maintaining tissue levels of cGMP, were determined in the ovaries of rabbits killed without treatment or 4 h after administration of luteinizing hormone [ **LH**]. Ovarian activities of the 2 enzymes were determined in the 100,000 g supernatant fraction (cytosol) and the resulting pellet (particulate fraction). Significant phosphodiesterase and cyclase activities were detected in both the cytosol and particulate fractions. Administration of **LH** had no significant effect on phosphodiesterase activity in either of the tissue fractions. **LH** caused a significant drop in guanylate cyclase activity in the cytosol and particulate fractions. This drop in the cyclase activity may be the cause of the decreased rabbit ovarian concentrations of cGMP previously observed after **LH** stimulation.

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ACCESSION NUMBER: 1981:205770 BIOSIS  
DOCUMENT NUMBER: PREV198171075762; BA71:75762  
TITLE: TUNGSTATE STIMULATES ADENYLATE CYCLASE EC-4.6.1.1.

AUTHOR(S): HWANG P L [Reprint author]; RYAN R J

CORPORATE SOURCE: DEP OF CELL BIOL, MAYO CLINIC AND MAYO MED SCH,  
ROCHESTER, MINN 55901, USA

SOURCE: Endocrinology, (1981) Vol. 108, No. 2, pp. 435-439.

CODEN: ENDOAO. ISSN: 0013-7227.

DOCUMENT TYPE: Article

FILE SEGMENT: BA

LANGUAGE: ENGLISH

AB Tungstate stimulates adenylate cyclase in ovarian homogenates of the rat; maximal stimulation (.apprx. 3-fold) is achieved at a concentration of 1 mM. This stimulation of cAMP production cannot be explained by the inhibition of phosphodiesterase activity or of ATP hydrolysis. Activation of adenylate cyclase by tungstate is rapid and reversible. The effects of tungstate and hCG [human chorionic gonadotropin] on

cyclase activity are additive, but tungstate does not augment fluoride-stimulated activity. At higher concentrations (5 and 10 mM), tungstate inhibits basal as well as hCG- and fluoride-stimulated cyclase activity in an irreversible manner. After solubilization by Lubrol-PX, the cyclase enzyme is inhibited by tungstate at concentrations ranging 0.1-10 mM. Tungstate also activates adenylate cyclase in the brain, heart, lungs, kidneys and liver of the rat. Tungstate activation of adenylate cyclase may be a general phenomenon and may be mediated by a similar mechanism in different tissues. Tungstate provides an additional tool by which the molecular basis of adenylate cyclase activation can be probed.

L64 ANSWER 40 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation  
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ACCESSION NUMBER: 1981:132037 BIOSIS  
DOCUMENT NUMBER: PREV198171002029; BA71:2029  
TITLE: EFFECTS OF MAMMALIAN GONADOTROPINS ON PROGESTERONE  
RELEASE AND CYCLIC NUCLEOTIDE PRODUCTION BY ISOLATED  
AVIAN GRANULOSA CELLS.  
AUTHOR(S): HAMMOND R W [Reprint author]; TODD H; HERTELENDY F  
CORPORATE SOURCE: ST LOUIS UNIV MED CENT, 1325 S GRAND BLVD, ST LOUIS, MO  
63104, USA  
SOURCE: General and Comparative Endocrinology, (1980) Vol. 41,  
No. 4, pp. 467-476.  
CODEN: GCENA5. ISSN: 0016-6480.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB CAMP and, to a lesser extent, cGMP were implicated as mediators of gonadotropin-induced steroidogenesis in ovarian tissue and cells of mammals. The functional role of these cyclic nucleotides in steroidogenesis in avian granulosa cells was not investigated. Progesterone release and levels of cyclic nucleotides were measured in granulosa cells isolated by a nonenzymatic procedure from the largest preovulatory follicle of laying hens 22-24 h prior to ovulation. Bovine [b] LH [lutropin] (NIH-B10) promoted progesterone production in a dose-related manner. Although steroidogenesis was maximally stimulated by 0.1-0.2 µg/ml bLH, cyclic nucleotide levels remained unaffected even at 5 µg/ml bLH at which concentration progesterone release was significantly inhibited when compared to maximal responses. Similarly, ovine follitropin while stimulating steroidogenesis, although less effectively than bLH, failed to significantly increase cAMP production. Theophylline potentiated the steroidogenic effect of gonadotropins and raised basal levels of the cyclic nucleotides. Dibutyryl cAMP (BU2cAMP) induced a dose-dependent release of progesterone while BU2GMP had an inhibitory effect. Agonists of adenylate cyclase such as isoproterenol and cholera toxin in combination with theophylline stimulated progesterone production while heparin, an inhibitor of adenylate cyclase, completely blocked the steroidogenic effect of bLH. Imidazole, a phosphodiesterase activator, suppressed both progesterone and cAMP production. A small fraction of intracellular cAMP, but not cGMP, which cannot be accurately detected by the radioimmunoassay method employed, plays an important role in LH-promoted steroidogenesis in chicken granulosa cells.

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ACCESSION NUMBER: 1980:209429 BIOSIS  
 DOCUMENT NUMBER: PREV198070001925; BA70:1925  
 TITLE: CYCLIC AMP PROSTAGLANDIN E-2 AND STEROIDS POSSIBLE  
 MEDIATORS IN THE RAT CUMULUS OOPHORUS MUCIFICATION.  
 AUTHOR(S): DEKEL N [Reprint author]; PHILLIPS D M  
 CORPORATE SOURCE: DEP BIOL, NY UNIV, NEW YORK, NY 10003, USA  
 SOURCE: Biology of Reproduction, (1980) Vol. 22, No. 2, pp.  
 289-296.  
 CODEN: BIREBV. ISSN: 0006-3363.

DOCUMENT TYPE: Article  
 FILE SEGMENT: BA  
 LANGUAGE: ENGLISH

AB The possible role of cyclic[c]AMP, prostaglandin [PG] E2, progesterone [P] and estradiol-17 $\beta$  [E2] in in vitro induction of the rat cumulus oophorus mucification was studied with the scanning electron microscope. **Follicular** cumulus-oocyte complexes were isolated at early proestrus and cultured for 24 h. cAMP levels in the incubated complexes were elevated by addition of cAMP derivatives (dibutyryl cAMP or 8-bromo-cAMP), the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (MIX), or the adenylate cyclase **stimulator**, cholera enterotoxin. Under all these culture conditions the cumulus cells were stimulated to secrete a hyaluronidase-sensitive mucoid material which coated the cumulus-oocyte complexes. These complexes were similar in appearance to those incubated in the presence of gonadotropins. In the absence of the above agents extracellular material was not observed. In vitro cumulus mucification was not induced by PGE2; indomethacin, an inhibitor of PG synthetase, failed to block mucification in complexes that were incubated in the presence of LH [lutropin]. Cumulus complexes were not stimulated to mucify in vitro by P or E2. Therefore, the response of the cumulus cells to the gonadotropic stimulus appears to be mediated by cAMP. PGE2 and steroids seem not to be involved in this process.

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ACCESSION NUMBER: 1981:163501 BIOSIS  
 DOCUMENT NUMBER: PREV198171033493; BA71:33493  
 TITLE: PROLONGATION OF THE EFFECTS OF GONADOTROPINS AND  
 PROSTAGLANDIN E-2 ON OVARIAN CYCLIC AMP FORMATION BY  
 INHIBITORS OF PROTEIN SYNTHESIS.  
 AUTHOR(S): BERGH C [Reprint author]; AHREN K  
 CORPORATE SOURCE: DEP PHYSIOL, UNIV GOTEBOG, SWED  
 SOURCE: Acta Endocrinologica, (1980) Vol. 94, No. 2, pp.  
 251-258.  
 CODEN: ACENA7. ISSN: 0001-5598.

DOCUMENT TYPE: Article  
 FILE SEGMENT: BA  
 LANGUAGE: ENGLISH

AB The effects of LH [lutropin], FSH [follitropin] and PG[prostaglandin]E2 on the accumulation of cAMP by isolated whole ovaries from 23-24 day old rats were studied in time-course experiments in the presence and absence of 2 inhibitors of protein synthesis, puromycin and cycloheximide. In absence of these inhibitors ovarian cAMP levels reached peak levels within 30 min for all **stimulators** and returned towards **pre-stimulation** levels within 2-4 h. When puromycin (500  $\mu$ g/ml) or cycloheximide (5  $\mu$ g/ml) was present together with LH, FSH or PGE2, respectively, ovarian cAMP levels

did not decrease after the initial peak but remained high for the entire incubation period (4-5 h). The release of cAMP to the incubation medium was much higher when puromycin or cycloheximide was present, illustrating that the effect of puromycin and cycloheximide was not caused by an inhibition of the cAMP release. The effects of puromycin and cycloheximide were, in principle the same when a phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine, was present. In the ovary there are either proteins with very rapid turn-over, necessary for the mechanism leading to refractoriness of the cAMP system, or the gonadotropins and PGE2 as an early effect stimulate the production of a specific protein necessary for the development of refractoriness.

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ACCESSION NUMBER: 1981:174559 BIOSIS  
DOCUMENT NUMBER: PREV198171044551; BA71:44551  
TITLE: INHIBITION OF LUTEINIZING HORMONE  
STIMULATED CYCLIC AMP FORMATION IN PRE  
OVULATORY RAT GRANULOSA CELLS BY  
FOLLICULAR FLUID.  
AUTHOR(S): NORDENSTROM K [Reprint author]; SJOGREN A; HAMBERGER L  
CORPORATE SOURCE: DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF GOTEBOG,  
MEDICINAREGATAN 11, S-400 33 GOTEBOG, SWEDEN  
SOURCE: Acta Endocrinologica, (1980) Vol. 95, No. 1, pp. 84-89.  
CODEN: ACENA7. ISSN: 0001-5598.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB Immature female rats were injected s.c. with a single dose of PMSG [pregnant mare serum gonadotropin] to induce growth and maturation of ovarian follicles. In the morning of proestrus the rats were given a single i.p. injection of LH [luteinizing hormone, lutropin] (10 µg/rat) or 0.154 M NaCl, 2 h prior to sacrifice. Granulosa cells were isolated from the pre-ovulatory follicles and incubated in Krebs bicarbonate buffer, for 1 h with or without in vitro addition of various test substances. Following incubation the amounts of cAMP in tissue plus medium were determined. Isolated granulosa cells exposed to LH in vivo responded to the addition of LH in vitro with a production of high amounts of cAMP, i.e., these cells were not refractory to LH stimulation and in fact responded better than granulosa cells isolated from ovaries not exposed to LH in vivo. The addition to the incubation medium of follicular fluid (FFI) obtained from pre-ovulatory follicles decreased the effect of LH in vitro when added at a final concentration of 1% and completely abolished it at a concentration of 3%. Removal of steroids from the FFI did not influence the inhibitory effect and the addition of a phosphodiesterase inhibitor (IBMX [isobutylmethylxanthine]) in vitro did not alter the results in principle. These results point to the existence of a factor in the FFI which interacts with the sensitivity of the isolated preovulatory granulosa cells to repeated exposures to LH.

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ACCESSION NUMBER: 1981:174558 BIOSIS  
DOCUMENT NUMBER: PREV198171044550; BA71:44550  
TITLE: DISCREPANCY BETWEEN THE EFFECTS OF DESIALYLATION OF

HUMAN CHORIONIC GONADOTROPIN ON  
IN-VITRO OVARIAN BIOLOGICAL ACTIVITY AND ON RECEPTOR  
BINDING.

AUTHOR(S): BRAND E C [Reprint author]; ODINK J; VAN HALL E V  
CORPORATE SOURCE: DEPARTMENT OF CHEMICAL PATHOLOGY, UNIVERSITY HOSPITAL,  
LEIDEN, THE NETHERLANDS  
SOURCE: Acta Endocrinologica, (1980) Vol. 95, No. 1, pp. 75-83.  
CODEN: ACENA7. ISSN: 0001-5598.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB An in vitro bioassay based on progesterone production by enzymatically-dispersed immature rat ovary cells, was used to investigate the effect of sialidase treatment on the biological activity of human **chorionic gonadotropin** (**hCG**). The potency in this bioassay system and in an ovarian receptor assay were compared, to substantiate possible discrepancies between the effect of this treatment on biological activity and on receptor binding. Ovarian cells responded dose-dependently to the addition of **hCG** as well as sialidase treated **hCG** (**asialo-hCG**). Dose-response curves of **hCG** and **asialo-hCG** were parallel and the maximal stimulation levels reached were the same. Sub-maximal dose of **hCG** and **asialo-hCG** were additive. The potency of **asialo-hCG** was 65% of the original preparation. Addition of low concentrations of phosphodiesterase inhibitor [isobutylmethylxanthine] resulted in a greatly enhanced sensitivity of the bioassay, but had no effect on the potencies of **asialo-hCG** and **hCG**. In contrast to intact gonadotropins, the receptor assay potency of **asialo-hCG** was more than 3 times the bioassay potency. In agreement with this, it was found that when equal amounts of 125I-labeled **hCG** and **asialo-hCG** were specifically bound to the **ovarian** cells, the latter **stimulated** progesterone production less effectively. There evidently is a discrepancy between the effect of desialylation on the biological activity and on the receptor-binding ability of **hCG**.

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ACCESSION NUMBER: 1979:225324 BIOSIS  
DOCUMENT NUMBER: PREV197968027828; BA68:27828  
TITLE: GONADOTROPIN ACTION IN ISOLATED **OVARIAN**  
LUTEAL CELLS THE INTERMEDIATE ROLE OF CYCLIC AMP IN  
HORMONAL **STIMULATION** OF PROGESTERONE  
SYNTHESIS.  
AUTHOR(S): SALA G B [Reprint author]; DUFAU M L; CATT K J  
CORPORATE SOURCE: ENDOCRINOL REPROD RES BRANCH, NATL INST CHILD HEALTH  
HUM DEV, NATL INST HEALTH, BETHESDA, MD 20014, USA  
SOURCE: Journal of Biological Chemistry, (1979) Vol. 254, No.  
6, pp. 2077-2083.  
CODEN: JBCHA3. ISSN: 0021-9258.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB There is a marked dissociation between cyclic[c]AMP formation and progesterone production in **ovarian** luteal cells **stimulated** by gonadotropin concentrations that elicit a dose-related increase in steroidogenesis. This apparent disparity was analyzed by measurement of cAMP production and binding to

intracellular receptors during hormonal stimulation of isolated luteal cells by human chorionic gonadotropin (hCG). During kinetic studies in the presence of 1 and 20 pM hCG, both intracellular and receptor-bound cAMP were increased within 5 min after addition of gonadotropin and progesterone synthesis increased progressively after 10 min. During dose-response studies with 0.2-200 pM hCG, the occupancy of cAMP receptors by endogenous nucleotide rose progressively over a 2-fold range to almost full saturation, while intracellular cAMP rose 3-fold and extracellular cAMP rose 500-fold. The progesterone response to hCG was coincident with the progressive elevations of bound, intracellular and extracellular cAMP throughout the range of the dose-related increase in steroidogenesis. Measurement of the simultaneous decrease in free receptor sites by c[3H]AMP binding studies was precluded by the rapid dissociation of cAMP from its receptor ( $K_d = 1.15 \times 10^{-2} \text{ min}^{-1}$ ) and the relatively slow association rate constant ( $k_a = 8.8 \times 10^5 \text{ M}^{-1} \text{ min}^{-1}$ ). The receptor affinity constant ( $K_a$ ) derived from equilibrium binding studies with c[3H]AMP was  $1.7 \times 10^8 \text{ M}^{-1}$ . Incubation of luteal cells with 0.2 mM methyl-3-isobutylxanthine decreased the ED50 for hormone stimulation by 50%, and in kinetic studies reduced the delay in progesterone production from 20 to 5 min. The actions of 1-methyl-3-isobutylxanthine on cAMP formation were largely confined to the extracellular nucleotide and did not produce consistent changes in intracellular and receptor-bound cAMP that would account for the increased sensitivity of the progesterone response to gonadotropin in the presence of phosphodiesterase inhibitors. cAMP evidently plays a role in hormonal activation by hCG at concentrations that produced dose-related increases in progesterone formation.

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ACCESSION NUMBER: 1980:161418 BIOSIS  
DOCUMENT NUMBER: PREV198069036414; BA69:36414  
TITLE: REGULATION OF ORNITHINE DECARBOXYLASE IN ISOLATED GRANULOSA CELLS IN-VITRO BY CONSTITUENTS OF FOLLICULAR FLUID.  
AUTHOR(S): VELDHUIS J D [Reprint author]; DEMERS L M; HAMMOND J M  
CORPORATE SOURCE: ENDOCRINE DIV, DEP MED, MILTON S HERSHEY MED CENT, PA STATE UNIV, HERSHEY, PA 17033, USA  
SOURCE: Endocrinology, (1979) Vol. 105, No. 5, pp. 1143-1151.  
CODEN: ENDOAO. ISSN: 0013-7227.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB Follicular fluid pooled from small follicles (FFs) of sexually immature pigs was examined for regulatory properties utilizing hormonally responsive porcine granulosa cells under serum-free conditions in vitro. FFs contains heat-labile ornithine decarboxylase (ODC)-stimulating factors equipotent with FSH [follitropin], LH [lutropin] or prostaglandin (PG)E<sub>2</sub>. Significant activity is preserved after extensive dialysis or 99.5% adsorption of steroids by charcoal. ODC stimulation by submaximal concentrations of FFs is additive to that of saturating doses of LH, FSH, PGE<sub>2</sub>, or epidermal growth factor. Maximal concentrations of FFs exhibit synergism with saturating levels of FSH, LH or PGE<sub>2</sub> in ODC stimulation. Preliminary MW sizing of the FFs-stimulating activity by membrane ultrafiltration revealed 2 active fractions with discrete, saturable,

concentration-dependent responses: a high MW substance (> 300,000 daltons), and a low MW moiety (< 10,000 daltons) stable after lyophilization. No activity was detectable in the 10,000-300,000 dalton fraction after 4-fold concentration. The mechanism of FFs action was studied. The relationship of c[cyclic]AMP to FFs-stimulated ODC activity is complex. The phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (0.25 mM), significantly potentiates stimulation of ODC by FFs. The effects of maximally stimulating concentrations of 8-bromo-cAMP (0.5 mM) are additive to those of FFs. Further analysis of the active fractions of FFs indicated that enhancement of maximal 8-bromo-cAMP stimulation occurred with the < 10,000 dalton moiety but not with the > 300,000 dalton fraction. Similarly, 3-isobutyl-1-methylxanthine enhancement occurred with the high rather than the low MW moiety. Thus, the action of the < 10,000 (but not the > 300,000) dalton fraction appears independent of cAMP. Further investigation of the mechanism of ODC stimulation by FFs demonstrated that cycloheximide (10 µg/ml) reduced ODC augmentation by FFs to undetectable assay levels; actinomycin D (1 µg/ml) and α-amanitin (1 µg/ml) diminished ODC activity to below unstimulated control levels. To assess possible post-translational enzyme stabilization, the t<sub>1/2</sub> [half-life] of enzyme activity decay after 95% protein synthesis inhibition with cycloheximide was studied. ODC activity decreased with a t<sub>1/2</sub> of 44.7 min after follicular fluid stimulation and 41.7 min after supramaximal FSH. FFs contains heat-labile nonsteroidal factors capable of stimulating ODC activity in isolated granulosa cells under serum-free conditions in vitro. These factors apparently differ from other well characterized stimulators of ODC in this cell system and the mechanism of action of 1 moiety may be independent of cAMP.

L64 ANSWER 47 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1979:238097 BIOSIS  
DOCUMENT NUMBER: PREV197968040601; BA68:40601  
TITLE: RECEPTOR MEDIATED GONADOTROPIN ACTION IN THE OVARY  
REGULATORY ROLE OF CYCLIC NUCLEOTIDE PHOSPHO DI  
ESTERASE IN INTRA CELLULAR CYCLIC AMP TURNOVER  
GONADOTROPIN STIMULATED PROGESTERONE  
PRODUCTION BY RAT OVARIAN CELLS.  
AUTHOR(S): AZHAR S [Reprint author]; MENON K M J  
CORPORATE SOURCE: ENDOCR LAB, DEP OBSTET, UNIV MICH MED SCH, ANN ARBOR,  
MICH 48109, USA  
SOURCE: Biochemical Journal, (1979) Vol. 180, No. 1, pp.  
201-212.  
ISSN: 0264-6021.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH  
AB The regulatory role of cyclic nucleotide phosphodiesterase(s) and cyclic[c]AMP metabolism in relation to progesterone [P] production by gonadotropins was studied in isolated rat ovarian cells. Low concentrations of choriogonadotropin (CG, 0.4-5 ng/ml) increased steroid production without any detectable increase in cAMP when experiments were carried out in the absence of phosphodiesterase inhibitors. The concentration of CG (10 ng/ml) that stimulated P synthesis maximally resulted in a minimal increase in cAMP accumulation and CG binding. CG at a concentration of 10 ng/ml and higher, however, significantly stimulated protein kinase activity and

reached a maximum between 250 and 1000 ng of hormone/ml. Higher concentrations (50-2500 ng/ml) of CG caused an increase in endogenous cAMP. This increase preceded the increase in steroid synthesis. Analysis of dose-response relationships of gonadotropin-stimulated cAMP accumulation, P production and protein kinase activity revealed a correlation between these responses over a wide concentration range when experiments were performed in the presence of 3-isobutyl-1-methylxanthine. The phosphodiesterase inhibitors papaverine, theophylline and 3-isobutyl-1-methylxanthine each stimulated steroid production in a dose-dependent manner. Incubation of ovarian cells with dibutyryl [db] cAMP or 8-bromo cAMP mimicked the steroidogenic action of gonadotropins and this effect was dependent on incubation time and nucleotide concentration. Maximum stimulation was obtained with 2 mM-dbcAMP and 8-bromo cAMP. This increase was close to that produced by a maximally stimulating dose of CG. Other 8-substituted derivatives such as 8-hydroxy cAMP and 8-isopropylthio cAMP, which were less susceptible to phosphodiesterase action, also effectively stimulated steroidogenesis. The uptake and metabolism of [3H]cAMP in ovarian cells was also studied in relation to steroidogenesis. When ovarian cells were incubated for 2 h in the presence of increasing concentrations of [3H]cAMP, the radioactivity associated with the cells increased almost linearly up to 250  $\mu$ M [3H]cAMP concentration in the incubation medium. The 3H label in the cellular extract was recovered mainly in the forms ATP, ADP, AMP, adenosine and inosine, with cAMP accounting for less than 1% of the total tissue radioactivity. Incubation of cAMP in vitro with ovarian cells resulted in a rapid breakdown of the nucleotide in the medium. The degradation products in the medium were identified as AMP, adenosine and inosine. The rapid degradation of cAMP by phosphodiesterase(s) makes it difficult to correlate changes in cAMP concentrations with steroidogenesis. These observations thus provide an explanation for the previously observed lack of cAMP accumulation under conditions in which low doses of CG stimulated steroidogenesis without any detectable changes in cAMP accumulation.

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ACCESSION NUMBER: 1979:231522 BIOSIS  
DOCUMENT NUMBER: PREV197968034026; BA68:34026  
TITLE: HORMONALLY INDUCED CELL SHAPE CHANGES IN CULTURED RAT  
OVARIAN GRANULOSA CELLS.  
AUTHOR(S): LAWRENCE T S [Reprint author]; GINZBERG R D; GILULA N  
B; BEERS W H  
CORPORATE SOURCE: ROCKEFELLER UNIV, NEW YORK, NY 10021, USA  
SOURCE: Journal of Cell Biology, (1979) Vol. 80, No. 1, pp.  
21-36.  
CODEN: JCLBA3. ISSN: 0021-9525.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB Cultured rat ovarian granulosa cells undergo a dramatic morphological change when exposed to follicle-stimulating hormone (FSH). Exposure to FSH caused the flattened epithelioid granulosa cells to assume a nearly spherical shape while retaining cytoplasmic processes which contact the substrate as well as adjacent cells. This effect of FSH was preceded by a dose-dependent increase in intracellular c[cyclic]AMP, was potentiated by cyclic nucleotide phosphodiesterase inhibitors and was mimicked by dibutyryl cAMP. Prostaglandins E1 or



E2 and cholera enterotoxin also caused the cells to change shape. A subpopulation of the cells responded to **luteinizing hormone**. These morphological changes, which were blocked by 2,4-dinitrophenol, resemble those produced by treating cultures with cytochalasin B. EM showed that the unstimulated, flattened cells contain bundles of microfilaments particularly in the cortical and basal regions. After **FSH** stimulation, microfilament bundles were not found in the rounded granulosa cell bodies but they were present in the thin cytoplasmic processes. The morphological change apparently results from a cAMP-mediated, energy-dependent mechanism that may involve the alteration of microfilaments in these cells.

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ACCESSION NUMBER: 1979:29805 BIOSIS  
DOCUMENT NUMBER: PREV197916029805; BR16:29805  
TITLE: PROLONGATION OF THE EFFECT OF **FOLLICLE STIMULATING HORMONE** ON **OVARIAN** CYCLIC AMP FORMATION BY CYCLO HEXIMIDE.  
AUTHOR(S): BERGH C; SELSTAM G; AHREN K  
SOURCE: (1978) pp. 773. GEORGE, WILLIAM J. AND LOUIS J. IGNARRO (ED.). ADVANCES IN CYCLIC NUCLEOTIDE RESEARCH, VOL. 9. THIRD INTERNATIONAL CONFERENCE ON CYCLIC NUCLEOTIDES. NEW ORLEANS, LA., USA, JULY 17-22, 1977. XXXII+799P. ILLUS. RAVEN PRESS: NEW YORK, N.Y., USA. ISBN 0-89004-240-3.  
DOCUMENT TYPE: Book  
FILE SEGMENT: BR  
LANGUAGE: Unavailable

L64 ANSWER 50 OF 56 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation  
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ACCESSION NUMBER: 1979:167177 BIOSIS  
DOCUMENT NUMBER: PREV197967047177; BA67:47177  
TITLE: GONADOTROPIN **STIMULATION** OF PORCINE **OVARIAN** ORNITHINE DECARBOXYLASE EC-4.1.1.17 IN IN-VITRO THE ROLE OF CYCLIC AMP.  
AUTHOR(S): OSTERMAN J [Reprint author]; DEMERS L M; HAMMOND J M  
CORPORATE SOURCE: DIV ENDOCRINOL, MILTON S HERSHEY MED CENT, HERSHEY, PA 17033, USA  
SOURCE: Endocrinology, (1978) Vol. 103, No. 5, pp. 1718-1724. CODEN: ENDOAO. ISSN: 0013-7227.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB The role of c[cyclic]AMP as a mediator [lutropin] of gonadotropin **stimulation** of **ovarian** ornithine decarboxylase (ODC) activity was studied in granulosa cells isolated from small (1-2 mm) porcine **ovarian** follicles. These cells responded to both **FSH** [**follicle stimulating hormone**] and **LH** [lutropin] with significant increases in intracellular concentration of cAMP. At concentrations of gonadotropins which were saturating for the induction of ODC activity, **FSH** was a more potent stimulator of both cAMP production and ODC activity than **LH**. N,O'-Dibutyryl cAMP (1.0-10.0 mM) caused a dose-dependent stimulation of ODC activity which equaled the maximal effect of **LH** but was significantly less effective than the saturating dose of **FSH**. 8-Bromo-cAMP was more potent than N,O'-dibutyryl cAMP and as effective as **FSH** as an inducer of ODC activity. Addition

of theophylline, a phosphodiesterase inhibitor, to the incubation medium resulted in a dose-dependent inhibition of ODC activity in both control and gonadotropin-stimulated cells. 1-Methyl,3-isobutyl xanthine, another phosphodiesterase inhibitor, potentiated effects of both submaximal and maximal effective doses of gonadotropins while producing no effect on basal ODC activity of these cells. cAMP can mediate gonadotropin stimulation of ODC in porcine granulosa cells. The importance of proper selection of cAMP analogs and phosphodiesterase inhibitors, and their concentration studying such effects is shown.

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ACCESSION NUMBER: 1979:141288 BIOSIS  
DOCUMENT NUMBER: PREV197967021288; BA67:21288  
TITLE: INTERACTIONS OF GONADOTROPINS WITH CORPUS LUTEUM MEMBRANES PART 2 THE IDENTIFICATION OF 2 DISTINCT SURFACE MEMBRANE FRACTIONS FROM SUPER OVULATED RAT OVARIES.  
AUTHOR(S): BRAMLEY T A [Reprint author]; RYAN R J  
CORPORATE SOURCE: DEP MOL MED, MAYO CLIN MAYO FOUND, GUGGENHEIM BUILD, ROCHESTER, MINN 55901, USA  
SOURCE: Endocrinology, (1978) Vol. 103, No. 3, pp. 796-804. CODEN: ENDOAO. ISSN: 0013-7227.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BA  
LANGUAGE: ENGLISH

AB Fractions enriched in hCG[human chorionic gonadotropin]-binding activity were prepared by differential rate centrifugation of superovulated rat ovarian homogenates and were applied to continuous sucrose density gradients (20-55%). After centrifugation at 63,000 + g for 3.5 h, fractions of each gradient were collected and assayed for a range of marker enzyme activities characteristic of surface membranes and subcellular organelles. Mitochondria, lysosomes, and rough and smooth endoplasmic reticulum membranes accumulated in the gradient between 38-41% sucrose (1.165-1.180 g/cm<sup>3</sup>). Nuclei passed through the gradient. The various surface membrane markers concentrated in 2 distinct regions of the gradient. Alkaline phosphatase, phosphodiesterase, (Na<sup>+</sup> + K<sup>+</sup>)ATPase I, and hCG-binding activity concentrated at 29-32% sucrose (1.120-1.135 g/cm<sup>3</sup>), whereas 5'-nucleotidase, Mg<sup>2+</sup>-dependent ATPase, and adenylate cyclase activities (and minor peaks of hCG-binding and phosphodiesterase activities) were enriched at 36-38% sucrose (1.16-1.17 g/cm<sup>3</sup>). A 2nd ATPase, [(Na<sup>+</sup> + K<sup>+</sup>)ATPase II], was also observed in this region of the gradient, which could be distinguished from (Na<sup>+</sup> + K<sup>+</sup>)ATPase I of the light membrane fraction by its sensitivity to the Ca<sup>2+</sup>-chelating agent, ethylene glycol bis-(aminoethyl)tetraacetic acid (EGTA). The kinetics of binding of radioiodinated hCG to the gonadotropin receptors of the light and heavy membrane fractions were very similar. Fractionation of superovulated rat ovaries may yield 2 distinct populations of surface membrane material which have distinct densities and marker enzyme profiles. In contrast to the heavy membrane fraction, light membranes seem to possess considerable amounts of hCG receptor activity but very little adenylate cyclase.

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ACCESSION NUMBER: 1979:150196 BIOSIS

DOCUMENT NUMBER: PREV197967030196; BA67:30196  
 TITLE: PROSTAGLANDIN **STIMULATION OF OVARIAN**  
 ORNITHINE DECARBOXYLASE EC-4.1.1.17 IN-VITRO.  
 AUTHOR(S): OSTERMAN J [Reprint author]; HAMMOND J M  
 CORPORATE SOURCE: DIV ENDOCRINOL, DEP MED, MILTON S HERSHEY MED CENT,  
 HERSHEY, PA 17033, USA  
 SOURCE: Biochemical and Biophysical Research Communications,  
 (1978) Vol. 83, No. 3, pp. 794-799.  
 CODEN: BBRCA9. ISSN: 0006-291X.  
 DOCUMENT TYPE: Article  
 FILE SEGMENT: BA  
 LANGUAGE: ENGLISH  
 AB Prostaglandins [PG] E1 and E2 caused a 5-10 fold **stimulation**  
 of ornithine decarboxylase [EC 4.1.1.17] activity in granulosa cells  
 isolated from porcine **ovarian** follicles. The minimally  
 effective concentration of prostaglandin E2 was 10 ng/ml and the  
 plateau of activity was reached at 500 ng/ml. PGF2 $\alpha$  was  
 ineffective. 1-Methyl,3-isobutyl-xanthine, a phosphodiesterase  
 inhibitor, potentiated the effect of both submaximal and maximal  
 effective doses of PGE2, suggesting that the effect of PGE2 is  
 mediated by c[cyclic]AMP. The effect of PGE2 was similar to that of  
**luteinizing hormone** and a cAMP analog, 8-Bromo-cAMP.

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ACCESSION NUMBER: 1979:128336 BIOSIS  
 DOCUMENT NUMBER: PREV197967008336; BA67:8336  
 TITLE: ACUTE INFLUENCE OF **LUTEINIZING**  
**HORMONE AND FOLLICLE**  
**STIMULATING HORMONE ON CYCLIC AMP**  
**FORMATION IN ISOLATED GRANULOSA CELLS OF THE RAT.**  
 AUTHOR(S): HAMBERGER L [Reprint author]; NORDENSTROM K; ROSBERG S;  
 SJOGREN A  
 CORPORATE SOURCE: DEP PHYSIOL, UNIV GOTEBO, GOTEBOG, SWED  
 SOURCE: Acta Endocrinologica, (1978) Vol. 88, No. 3, pp.  
 567-579.  
 CODEN: ACENA7. ISSN: 0001-5598.  
 DOCUMENT TYPE: Article  
 FILE SEGMENT: BA  
 LANGUAGE: ENGLISH  
 AB A technique for the mechanical isolation of granulosa cells from the  
 rat ovary is described. Cyclic[c]AMP formation by the isolated  
 granulosa cells of the follicles in various stages of development was  
 studied in response to the administration in vitro of gonadotropins.  
 In granulosa cells from small to medium-sized follicles **FSH**  
 but not **LH** stimulated cAMP formation, while in cells from  
 pre-**ovulatory** follicles both gonadotropins had a stimulatory  
 effect. The effects of both gonadotropins were transient with a  
 maximal response after 15-60 min of incubation. In the presence of  
 the phosphodiesterase inhibitor, 3-isobutyl-methylxanthine, the action  
 of **FSH** was potentiated and prolonged while the response to  
**LH** was unaffected. Both gonadotropins activate the adenylate  
 cyclase system of the isolated granulosa cells while **FSH** in  
 addition stimulates the phosphodiesterase activity. Consecutive  
 determinations of cAMP during and after the pre-**ovulatory**  
**LH-FSH** surge, demonstrated a rise of cAMP levels in  
 granulosa cells from the pre-**ovulatory** follicles following  
 endogenous gonadotropin release. cAMP levels remained high or  
 increased until the time of **ovulation**.

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ACCESSION NUMBER: 1975:84717 BIOSIS  
DOCUMENT NUMBER: PREV197511084717; BR11:84717  
TITLE: CYCLIC NUCLEOTIDE INDUCED **STIMULATION** OF  
TESTOSTERONE PRODUCTION BY ISOLATED RABBIT  
**OVARIAN FOLLICLES.**  
AUTHOR(S): YOUNGLAI E V  
SOURCE: Endocrinology, (1975) Vol. 96, No. SUPPL, pp. 108.  
CODEN: ENDOAO. ISSN: 0013-7227.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BR  
LANGUAGE: Unavailable

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ACCESSION NUMBER: 1976:13087 BIOSIS  
DOCUMENT NUMBER: PREV197612013087; BR12:13087  
TITLE: EFFECTS OF INDOMETHACIN ON CYCLIC AMP PRODUCTION AND  
STEROID SECRETION BY RABBIT OVARIES IN-VIVO DURING THE  
PRE **OVULATORY** PERIOD.  
AUTHOR(S): GOFF A K; MAJOR P W  
SOURCE: Journal of Endocrinology, (1975) Vol. 65, No. 3, pp.  
23P.  
CODEN: JOENAK. ISSN: 0022-0795.  
DOCUMENT TYPE: Article  
FILE SEGMENT: BR  
LANGUAGE: Unavailable

L64 ANSWER 56 OF 56 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 74116493 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 4856151  
TITLE: Inhibitory effect of serotonin on **ovulation**  
in adult rats.  
AUTHOR: Wilson C A; McDonald P G  
SOURCE: Journal of endocrinology, (1974 Feb) 60 (2) 253-60.  
Journal code: 0375363. ISSN: 0022-0795.  
PUB. COUNTRY: ENGLAND: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 197405  
ENTRY DATE: Entered STN: 19900310  
Last Updated on STN: 19900310  
Entered Medline: 19740506

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